SEPTEMBER, 1950

BRAIN

VOL. 73, PART 3.

ADULT TOXOPLASMOSIS IN ONE FAMILY

BY

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TOXOPLASMOSIS has only recently been recognized in England. Jacoby (1948) and Wyllie *et alia* (1950) have described cases in young children. This paper is to emphasize the modified picture that may be shown in adult cases and to stress the familial side of the disease.

In animals the disease has been known since 1908, and has been found in many species. It occurs in rats, rabbits, dogs and squirrels and it is probable that animals infect man, although exactly how this occurs is unknown. The organism is a crescentic protozoon which can invade any tissue but has a predilection for the tissues of the nervous system and eye. The organism multiplies by simple-binary fission and is intracellular, sometimes forming groups or pseudo-cysts with clusters of organisms which may degenerate to form a necrotized granulomatous mass.

Although the organism was first described by Jankû (1923) most of the credit for investigating toxoplasmosis must be shared by Wolf *et alia* (1939) and Sabin (1942) in America. Wolf first demonstrated animal infection from human material and the congenital nature of the disease. Sabin has classified the disease into four main groups.

(i) Congenital.
(ii) Acquired disease in children.
(iii) Acquired disease in adults.
(iv) Latent disease with only pathological but no clinical findings.

The congenital cases show symptoms at birth and there may or may not be clinical evidence of the disease in the mother. Sabin has described a triad of symptoms that he considers important in the clinical diagnosis: hydrocephalus, cerebral calcification and choroido-retinitis. It is obvious that only one of these symptoms may be present and the case may still be one of toxoplasmosis. Callahan *et alia* (1946) found in St. Louis in 10,000 autopsies five cases of infantile toxoplasmosis which previously had passed unrecognized, and this is probably true of other cities. Apart from the

clinical recognition of the disease, diagnosis rests on the finding of the organism, which is extremely difficult, and on demonstration of the antibodies in the patient's serum. The value of the serological and pathological tests in this condition have been fully reviewed by Cathie and Dudgeon (1949). Evidence is now accumulating that many persons may show immune bodies to toxoplasmosis, and Sabin (1950) found figures as high as between 10 per cent and 60 per cent with positive serological tests in normal people in certain American cities. Before a diagnosis of toxoplasmosis can be reached it is necessary to weigh the clinical and pathological evidence most carefully.

The Disease In Adults

Sabin (1942) described an acquired form of the disease in older children, stressing the occurrence of acute encephalitis. As early as 1914 Castellani had claimed to have found an organism resembling toxoplasmosis in a Sinhalese boy of 14 years, dying of an unknown fever with splenomegaly and anæmia. Pinkerton and Henderson (1941) described an acute illness in adults which resembled typhus fever, in which there was a macular rash, pyrexia and pulmonary signs and in whom toxoplasma were demonstrated at the post-mortem. Their cases showed a resemblance to the Rickettsial diseases, and in both their cases was a history of a bite by a tick. In one of their patients the disease was successfully transmitted to guinea-pigs. Guimarâes (1943) described a young Brazilian negro who died of an acute meningo-encephalomyelitis at the age of 18. At post-mortem the patient showed extensive inflammatory areas throughout the brain from which toxoplasma were isolated.

Syverton and Slavin (1946) described an illness in a 65-year-old tailor with fever, diarrhœa and joint pains, a macular rash and a persistent eosinophilia of from 25 per cent to 45 per cent, and biopsy material from this case showed it to be a case of toxoplasmosis. This man had had an unexplained rash twenty-five years previously which may well have been a manifestation of toxoplasma infection. It suggested that the disease might remain latent for many years, and, as in the cases we propose to record, that fluctuations of the rash and suffusion of the eyes may have been an allergic reaction to toxoplasmosis antigen. Brennan (1949) has suggested that increase in the severity of the rash coincides with the release of new toxoplasma antigen from an internal focus. Binkhorst (1948) records in the mother of one of his cases the occurrence of a rash during her pregnancy which may have been due to toxoplasmosis, and the mother of the case recorded by Wyllie (1950) had a similar rash.

The familial side of this disease has not been adequately studied. The pathological tests have indicated that in affected infants and children the

mother has often shown either clinical signs of choroido-retinitis, which were previously undetected, or positive antibody reactions. Zuelzer (1944) has recorded the case of twins who suffered from the disease, and Robson (1950) has studied the case of a father and child who both had had a fever and encephalomyelitis, but the father's case history is somewhat indefinite and his case cannot be definitely regarded as one of toxoplasmosis, although several members of this family had choroido-retinitis and positive serological tests.

In the following family and in the adult cases previously recorded there is a pyrexial illness, with evidence of encephalomyelitis, rash, and possibly other neurological signs and eosinophilia.

CASE HISTORIES.—Cases 1 to 4 (with clinical signs of disease).

Case 1.—R. C., aged 19, a painter. Was first seen in March 1949, complaining of recurrent headaches for eight years. During the past year he had also noticed diminution in vision and had visited one of us (F. C.) who had noticed optic atrophy, slight swelling of the discs, peripheral choroido-retinitis (*see* Plate VIII), and opaque nerve fibres.

This boy gave a history that he had had a periodic maculo-papular rash ever since he could remember, and that he had also been subject to periodic joint pains and inflammation of the conjunctivæ. The swelling of the joints and the accompanying pains had been so bad at the age of 12 that he had been admitted to a Rheumatic Hospital as a case of acute rheumatism. He gave a family history that his sister suffered from somewhat similar symptoms, including the rash and headaches, and that his mother, whom he had not seen for twelve years as she was separated from his father, had often attended hospital for severe headaches and a rash.

On examination there was evidence of slight hydrocephalus and a saddleback nose, suggesting congenital syphilis. Apart from the eye changes previously stated, examination of the nervous system revealed bilateral nerve deafness, bilateral extensor plantar reflexes, a macular rash and suffusion of the eyes, which varied markedly from day to day, as did the severity of the headaches.

When first seen it was thought that this patient might be a case of congenital syphilis, and he was admitted for lumbar puncture in April 1949. The pressure was normal and the fluid normal, blood and cerebrospinal fluid Wassermann reaction were negative. Skull X-rays at this time suggested a minor hydrocephalus, but there was no intracerebral calcification. Chest X-ray was normal. No definite diagnosis was made, and at this stage toxoplasmosis was not considered.

In September 1949 this boy complained of even more severe headaches and had developed three dioptres of papillœdema. The patient was readmitted to hospital and the blood count done at this time showed a 7 per cent eosinophilia in a total white cell count of between 16,000 and 18,000. The patient had some pyrexia with a maximum diurnal rise to about 100° F., and the cerebrospinal fluid showed considerable pleocytosis, as high as 200 cells. There was a 10 per cent eosinophilia in the cerebrospinal fluid. Because of the association of meningo-encephalitis, eosinophilia, slight choroido-retinitis and macular rash, the patient's blood was sent to the Hospital for Sick Children, Great Ormond Street, for pathological tests for toxoplasmosis. These all proved to be positive.

The following additional tests were performed: Electro-encephalogram—grossly abnormal and suggestive of a deep-seated organic process with slow wave activity from both hemispheres. An electrocardiograph was normal. Blood Wassermann reaction was persistently negative on three occasions. Culture of the cerebrospinal fluid for torula was negative. Culture of the cerebrospinal fluid for tubercle bacilli

was negative. Agglutination tests for the typhoid group of organism were all negative: Paul Bunnell test was negative. As stated, X-rays of the skull showed slight hydrocephalus. An audiogram showed slight nerve deafness. Ventriculography was performed, and showed a generalized but slight increase in the size of the ventricles, and at the same time a biopsy of brain tissue was taken which was negative for toxoplasmosis. This material was also injected into rats, but even after passage, no evidence of toxoplasmosis infection was found when these animals were killed.

Various drugs were tried on this patient without success. Up to the time of writing we have tried, in succession, streptomycin, penicillin, aureomycin, emetine and sulphonamides, but none of these drugs has had any effect on the cerebrospinal cell count or the symptoms of the patient. Sulphonamides appeared to produce an exacerbation of the rash and rigors, followed by a temporary improvement of symptoms, indicating that they may have had some effect on the living organisms and produced an increased liberation of antigen. Unfortunately this patient still has severe headaches.

It was obvious that it was necessary to study further members of the family.

Case 2.—Mrs. C. (known as Mrs. P.), aged 49, mother of the first patient. It was extremely difficult to trace this lady as she was living apart from her husband with another man and, as will be seen, she was the illegitimate child of a lady who, by her promiscuity, has rendered follow-up of this family even more difficult. Mrs. C. was now aged 49 years and, as far as she can remember, had had a rash ever since birth. From her mother's statement there was doubt as to whether the rash was first noticed at birth or at 3 years of age. She was deaf as a child and in 1913, at the age of 12, she was admitted to the Bristol Royal Hospital as a case of unexplained meningitis. Unfortunately her notes were destroyed in the Bristol air raids, but in view of the history of the other members of the family, it is probable that she had an acute meningo-encephalitis at this period. Throughout her life she has noticed increasing deafness, a recurrent maculo-papular rash, severe headaches and an increasing defect in vision. The severity of her headaches had at times completely incapacitated her and throughout her life she had visited various doctors on account of her headaches, deafness and rash.

We visited this lady in her home at Leicester in March 1950, and found that she had attended the Rugby Hospital in 1949 complaining of headaches and had been admitted to hospital. The cerebrospinal fluid at this juncture contained 21 cells, 80 per cent lymphocytes, cerebrospinal protein 160 mg. per cent, with a paretic Lange curve and a negative Wassermann reaction. A cerebral abscess was suspected and she was transferred to the neurosurgical unit of the Birmingham United Hospital, where she was diagnosed as an atypical migraine and discharged. As far as we know no investigation except a lumbar puncture was done at Birmingham. In September 1949 she was readmitted to the Rugby Hospital with abdominal pain. Her gall-bladder was removed and contained a large stone. The surgeon told us he noticed at the time of the operation that the pancreas was large and hard, and he thought then that the patient might have chronic pancreatitis or a carcinoma of the pancreas. The liver was also enlarged and hard. The cerebrospinal fluid was examined at this time and was found to contain 7 cells (lymphocytes), and the protein was 110 mg. per cent. A blood count at this time showed an eosinophilia of 4 per cent and a microcytic anæmia. After the operation for

the removal of the gall-stone she developed a severe jaundice, the ætiology of which has not yet been finally explained.

On examination in March 1950 the patient showed a very severe degree of nerve deafness, extensive choroido-retinitis (*see* plates) and optic atrophy and a microcornea on the left, with the right pupil greater than the left. Both pupils reacted poorly to light and accommodation. There was evidence of a macular rash on the trunk and the limbs, slight enlargement of the liver and the spleen. There was also a saddleback nose as found in the son and daughter. Unfortunately the patient refused admission to Bristol and we could not carry out all the tests we would have wished, but X-rays of the skull done at Rugby showed no gross evidence of hydrocephalus or cerebral calcification. Serum complement-fixation test and cytoplasm modifying test were positive. It became evident that she had the same disease as her son.

In April 1950 her present husband, Mr. P., died from carcinoma of the bronchus. His blood had been previously examined and found to be negative to toxoplasmosis antibody tests, and a careful post-mortem examination showed no evidence of toxoplasma infection, so that there is no evidence that he contracted the infection from his wife.

Case 3.—Mrs. G., aged 26, daughter of Mrs. C. and sister of R. C. This lady very kindly consented to be admitted to hospital for investigation and had had very similar symptoms to her brother. She had had a maculo-papular rash since birth, and had been known to be severely deaf since the age of 10. This deafness has increased and since this age she has noticed increasingly severe headaches. The deafness had always been attributed to tonsillectomy. She had been married for four years, and had a child aged 3 who also showed a maculo-papular rash. On admission the main complaint was headache. The same fluctuation in the severity of the rash and the suffusion of the eyes was noticed as in her brother. There was considerable nerve deafness. Cerebrospinal fluid examination showed a cell count of 27, with a less marked pleocytosis and eosinophilia of 6 per cent. The cerebrospinal fluid protein was normal, 20 mg. per cent. Her cerebrospinal fluid pressure was slightly raised to 180 mm. of H_2O. On another occasion the lumbar puncture showed 100 cells, of which 4 per cent were eosinophils. Examination of the blood showed 4 per cent of eosinophils in a total white count of 7,500. There was no evidence of anæmia, and sedimentation rate was raised to 24 mm. in one hour. This patient had no pyrexia. X-rays of chest and skull were normal. There was some swelling of the optic disc, with the same peripheral choroido-retinitis as seen in her brother. Dilatation and curettage were performed on this patient to see whether toxoplasma would be found in the biopsy. The uterine endometrium was examined but no evidence of toxoplasmosis was found. The material was also injected into rats, with no success. Toxoplasmosis antibody tests were all positive as was the toxoplasmin skin test.

This patient was treated with aureomycin, sulphonamides and penicillin without any effect, apart from the same and somewhat more marked reactions to sulphathiazole as her brother. On the eighth day after the administration of this drug she developed a marked exacerbation of her rash, with rigors and a pyrexia up to 101° F., and it is obvious that the sulphathiazole in some way affected her condition. At the time of this reaction the spleen was enlarged and palpable for about two days. She was discharged from hospital after two months, still complaining of headaches.

Case 4.—G. G., aged 3, her child. She was also examined and found to show the same macular rash, but to be in every other way entirely healthy. Chest and skull X-ray were normal. The fundi were normal and, as far as could be ascertained, there was no deafness. The antibody tests were entirely negative, as also was the toxoplasmin test.

The clinical picture was the same in three members of this one family and this, with the positive pathological tests and despite our inability to find the organism, indicated that they were probably cases of toxoplasmosis.

It was important to try and prove whether any other members of this family showed evidence of the disease.

PATIENTS WITH NO CLINICAL EVIDENCE OF THE DISEASE (Cases 5 to 8)

Case 5.—Mrs. H., aged 73, the mother of Mrs. C. She was visited in Tunbridge Wells. On examination in her cottage she showed no clinical evidence of the disease. Her blood was also examined and the complement-fixation test was negative in her case, but the cytoplasm modifying test was positive: 1 in 8 on three occasions.

As can be seen from the family tree, p. 288, each of her five children was by a different man and it was impossible to trace these children for obvious reasons. Two of them are known to be in Canada, and she refused to give the addresses of the others living in this country. She did, however, give us the information that, at one stage of their lives, both she and her children lived in a mill which was infested with rats, and that the children when young kept rabbits.

Case 6.—Mrs. Po., aged 75, sister of Mrs. H. This lady was examined in her own home and found to be clinically fit apart from the fact that she was suffering from diabetes mellitus. Her pathological tests were also negative and she can be regarded as showing no evidence of the disease.

We now turn to two non-blood relations of this family.

Case 7.—Mr. C., father of R. C. and M. G., has very marked choroido-retinitis and a very high degree of myopia, otherwise his clinical examination was negative. The question arises as to whether his eye condition can be due to toxoplasma infection. The toxoplasmin test was slightly positive at 1:100. This reaction was not nearly so marked as in the other members of the family. The cytoplasm modifying test was positive, 1:64. The complement-fixation test was positive, 1:8.

Case 8.—Corporal G., husband of Mrs. G., shows no clinical evidence of the disease whatever. He shows, however, a weak positive toxoplasmin test at 1:100. His cytoplasm modifying antibody test was positive 1:24, and his complement-fixation test was positive 1:4.

It is probable that the husbands of the two clinical cases had developed sufficient antibody reaction to withstand severe infection.

COMMENTARY

This family has many unusual features. The picture of these cases can be compared to the behaviour of congenital syphilis, and there is evidence of transmission through three generations. It is impossible to

TABLE I

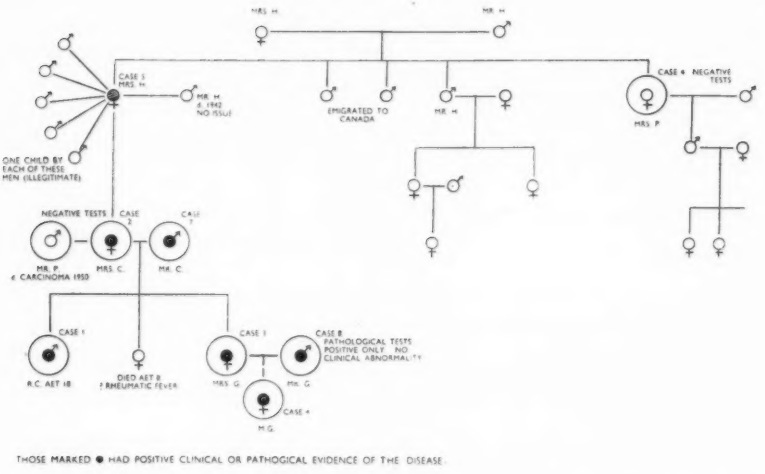
COMPARISON OF THREE MEMBERS MOST AFFECTED

	Mrs. C.	*R., her son*	*Mrs. G., her daughter*
Headache and sickness	+ since age of 5	++ since age of 8. Very acute recently	++ since age of 14
Rash (intermittent)	++	++	++
Suffusion of conjunctiva	++	++	++
Pyrexia	–	+	–
Saddleback nose	+	+	+
Claw feet	–	+	+
Joint pains	+	+	+
Cough	+	–	–
Hydrocephalus	–	+	+
		–	
Intracerebral calcification	–	–	–
Micro-ophthalmos	+	–	–
Micro-cornea	+	–	–
Choroido-retinitis	+++ macular and peripheral	+ slight peripheral	++ peripheral
Optic atrophy	++ severe	++	+
Papillœdema	–	++	+
Opaque nerve fibres	–	+	+
Nerve deafness	+++ severe	+	++
Meningo-encephalitis	++	++	+
Spasticity of legs	+	+	–
Extensor plantar reflex	+	+ bilateral	+ left only
Splenomegaly	+	–	+ temporary only
Wassermann Reaction	–	–	–
Blood	– ve ⎫ twice	– ve ⎫ five	– ve
C.S.F.	– ve ⎭	– ve ⎭ times	– ve
C.S.F. Pressure	Normal	300 mm. H_2O	Normal
Pleocytosis	20–30	80–190	20–30
Protein	110–160 mg. per cent	70–95 mg. per cent	20–65 mg. per cent
Eosinophilia			
Blood	4–8 per cent	10 per cent	4 per cent
C.S.F.	Unknown	5–10 per cent	6 per cent
Cytoplasm modifying test	+ at 1/32	+ at 1/128	+ at 1/32
Complement fixation test	+ at 1/8	8 times	+ at 1/16
	+ at 1/16	+ at 1/16	
		+ at 1/8	
Toxoplasmin skin test	not performed	+ 24 hours	+ 24 hours
		+ 48 hours	+ 48 hours

say with certainty whether the disease originated in the mother of the original patient, or his grandmother Mrs. H. (*see* family tree, Table II). This lady has shown one positive antibody test only. The infection has remained present in a subacute form in three members of one family, and possibly four, for many years, causing chronic ill-health, headaches and the

TABLE II

TOXOPLASMOSIS FAMILY



THOSE MARKED ● HAD POSITIVE CLINICAL OR PATHOGICAL EVIDENCE OF THE DISEASE

symptoms shown in Table II. It appears a state of chronic toxoplasma infection can exist in adults where the antibody response is insufficient to deal with the infection. In most persons infected the antibody response is obviously adequate, with the exception of the fœtus *in utero*, which is very liable to a severe and fatal infection. As yet we have no knowledge of how man may acquire the infection but it is becoming increasingly evident that dogs may become infected and their proximity to man makes them a most likely source of human infection. It is likely that the child G. G. (Case 4) may have the infection very mildly and had not yet developed any antibody response.

It may well be that certain persons are more susceptible to infection than others, and this would explain the large number of positive antibody tests in apparently healthy persons. The persistence or proliferation of toxoplasma in the eye and central nervous system may be explained by the poor diffusion of serum antibody into these tissues. The family we have recorded must have had a poor antibody response. It is likely that Mr. C. and Corporal G. acquired the infection without clinical manifestations, and thus antibody response was adequate. Mr. C. had marked choroido-retinitis, but it is open to question whether this was due to toxoplasmosis owing to his high degree of myopia. As has already been suggested, the continued release of antigen accounts for the rash, uveitis and eosinophilic response seen in our patients.

The case recorded by Brennan (1949) resembles this family most closely in that a man of 30 was found to have the same generalized cutaneous

eruption, choroido-retinitis and eosinophilia, with persistent but fluctuating headaches, with positive antibody tests and positive intradermal tests for toxoplasma antigen. This patient also had an intermittent fever, as shown by our patient, R. C. The eosinophilia was 4 per cent. This patient appeared to improve on sulphonamides, in the same way as R. C., but relapsed when they had to be discontinued due to hæmaturia. The authors stress the resemblance of the case to periarteritis nodosa, and erythema multiforme. As in our patients, the diagnosis of Brennan's case had to be on clinical grounds, and serological tests: but although we have failed to isolate the organism, we feel the whole picture presented by this remarkable family cannot be explained by any other ætiology. It must be emphasized that the antibody tests are merely confirmatory evidence of the clinical syndrome, and since speaking on this subject Symonds (1950) and Klinger (1950) have remembered unexplained cases resembling very closely the symptoms shown by this family. Other cases of this rare condition may be commoner than has hitherto been realized and cases showing symptoms in adult life may in fact be congenital, not acquired, infection.

The nerve deafness found in all these cases has not been previously recorded in toxoplasmosis, and it is important for aural specialists to bear toxoplasmosis in mind when examining cases of nerve deafness in children and young adults. The choroido-retinitis shown by these cases is much more slight and peripheral than the gross lesions seen in some cases where there is a large area of choroido-retinitis near the macula. The pepper and salt appearance of small lesions in our cases was much more marked in Mrs. C. than in her children. Therapy presents a most difficult problem as most drugs, with the possible exception of sulphonamides, have little effect on the organism. Frenkel (1949) has reported some improvement in retinal lesions, with graduated doses of toxoplasma antigen, and it might be worthy of trial in our case, R. C., but we fear that many of the changes in these chronic cases are irreversible. Our poor results of therapy are strictly in accord with other workers.

Summary

(1) A family showing a syndrome of chronic meningo-encephalitis, choroido-retinitis, rash, nerve deafness and eosinophilia is discussed.

(2) Reasons are given for the diagnosis of toxoplasmosis.

(3) Difficulties of therapy are discussed.

Acknowledgments

Our thanks are due to Dr. W. F. T. Tatlow for his assistance, Dr. W. D. Gillespie and Dr. I. A. B. Cathie for all the pathological work, Mr.

Alexander for his paintings of the fundi, and to Dr. Wakes Miller for data on Case 2. Finally we wish to acknowledge a grant for travelling expenses from the Bristol Royal Hospital Endowment Fund.

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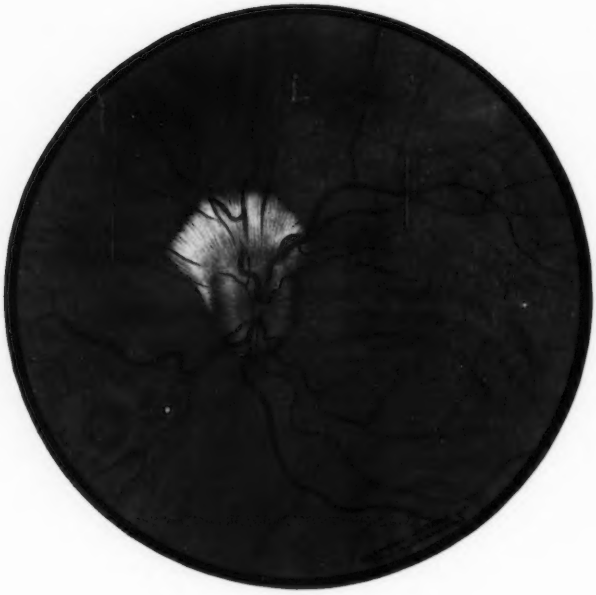
PLATE VII

Skin rash, Case 1.

Acute skin manifestations.

To illustrate article by A. M. G. Campbell and F. Clifton.

PLATE VIII

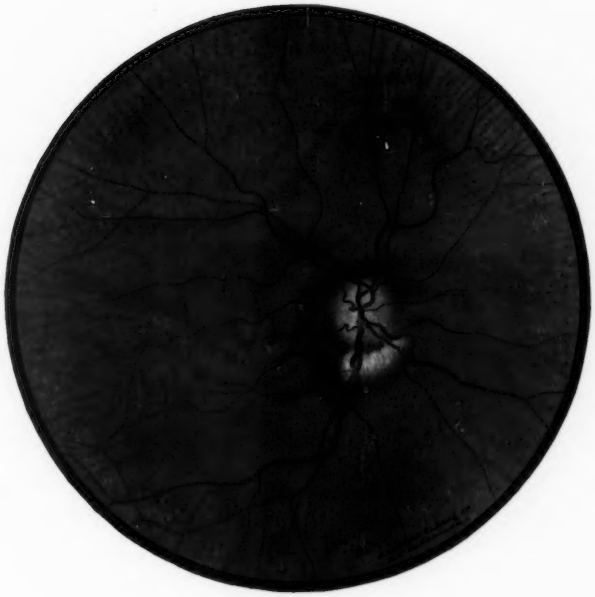


Case 1.—Left eye.

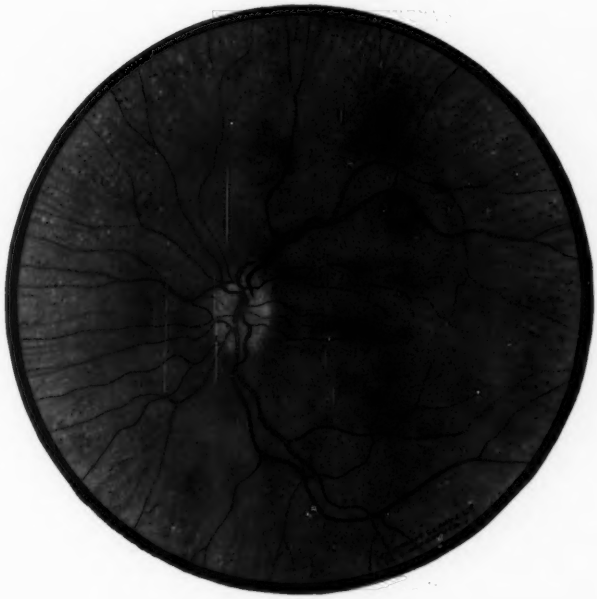
Case 2.—Right eye.

To illustrate article by A. M. G. Campbell and F. Clifton.

PLATE IX

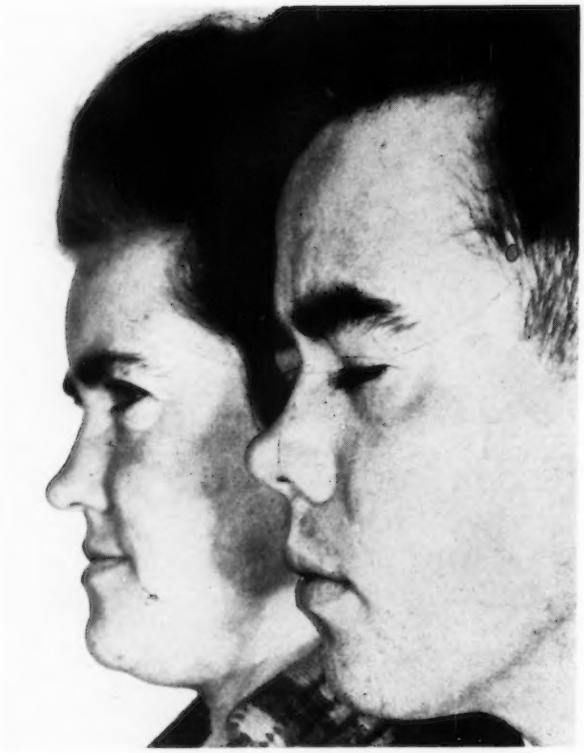


CASE 3.—Right eye.



CASE 3.—Left eye.

To illustrate article by A. M. G. Campbell and F. Clifton.



Facial appearance. Cases 1 and 3.

To illustrate article by A. M. G. Campbell and F. Clifton.

LATE INFANTILE METACHROMATIC LEUCO-ENCEPHALOPATHY, WITH PRIMARY DEGENERATION OF THE INTERFASCICULAR OLIGODENDROGLIA

BY

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UNDER the title "A form of progressive cerebral sclerosis in infants associated with primary degeneration of the interfascicular glia," one of us (Greenfield, 1933) recorded the clinical and pathological examinations of two children who died at the age of 3 years, after a progressive illness of twelve and eighteen months' duration. This began with unsteadiness in walking and progressed to complete dementia. Loss of vision came on in one child shortly before death. The post-mortem examination showed a very unusual form of demyelination of the white matter of the cerebral and cerebellar hemispheres, in which the brunt of the disease fell on the fibre systems which were unmyelinated at birth and incompletely myelinated at 3 months of age. Associated with this demyelination there were numerous "balls of mucinoid or other abnormal lipoid material," and complete disappearance of the interfascicular oligodendroglia, not only from areas which had lost their myelin completely, but also from areas where the process of demyelination was in a very early stage.

In the interval of fifteen years between the publication of these cases and the latest references available no further cases of the same kind have been found in the literature. The reasons for this may have been that in this form of diffuse sclerosis there is little or no evidence of demyelination of the white matter of the hemispheres on naked-eye examination, and that in paraffin sections no obvious abnormality may be apparent except loss of oligodendroglial nuclei and swelling of the astrocytes in the white matter. That it is not an extremely rare disease however is shown by the four further cases which form the basis of the present report. All occurred in the London area within a period of a little more than four years. The first case died in Chase Farm Emergency Hospital during the war, the third in the Westminster Hospital, where the pathologist recognized the condition as unusual and sent pieces of the brain to the laboratory of the National Hospital. The other two cases were examined at the National Hospital, Queen Square.

The accumulation of further knowledge about diffuse cerebral sclerosis in the interval since the publication of the two first cases, and especially the Danish monographs on the subject (Einarson and Neel, 1938, 1942, 1944), as well as the use of modern histo-chemical methods, have furthered the more complete histological examination which was made of these new cases. In addition to confirming the observations made in 1933 this has added certain new facts, especially the metachromasia to toluidin blue of some of the abnormal lipid, and the appearance of metachromatic products of metabolism in the liver and kidneys. The similarity of these six cases to one another, not only on the clinical side but, even more closely, on the pathological side, marks the condition as a special and well-defined form of infantile cerebral sclerosis.

Case 1.—The patient, B. H., was seen by the late Dr. George Riddoch on September 7, 1944, and the following notes were made by him at that time. The child was then aged 2 years and 10 months.

He was the only child of healthy parents. His birth had been normal and he weighed 7½ pounds at birth. There was no post-natal jaundice. He had at first progressed normally, and had been bright and intelligent; he spoke early and began to put words together at 10 months. He began to walk when 16 months old, at which time he had prophylactic injections against diphtheria (A.P.T.), but he was never very strong on his feet; he turned the left foot out in walking and fell very easily. When 19 months old he fell, hitting the left side of his head on concrete. He was a little dazed and frightened, but not unconscious. However, after this fall his walking gradually became worse, and four months before examination, i.e. at the age of 2½ years, he had become unable to walk or to stand. His right leg was weaker than his left. His arms were not affected at this date. There was no loss of control of the bladder. His back was weak so that if he fell he was unable to pull himself up into a sitting position.

Examination at this date showed a child who appeared spoilt and difficult to examine. The head was large. There was spontaneous nystagmus, but no other abnormality was found on examination of the cranial nerves. The pupils reacted well. The muscles of the neck, trunk and limbs were hypotonic with slight contracture of the flexors of the knees and of the calf muscles and marked weakness especially of the lower limbs. No tendon reflexes could be obtained and the plantar reflexes were also absent. The patient was sent to Chase Farm Hospital, Enfield, where he was admitted under the care of Dr. Russell Brain on October 11, 1944. Attacks in which he trembled all over had come on by this time, and he was perhaps less co-operative than on the previous examination, but talked fairly well. He could recognize objects such as a dog or a doll in pictures, and could be persuaded to obey simple commands. He was, however, now incontinent of urine and fæces.

The head measured 21 inches in circumference. There was no external evidence of spina bifida, but X-rays showed failure of union of the transverse processes of the fifth lumbar and first sacral vertebræ.

There was nystagmus and bilateral ptosis, otherwise movements of the external ocular muscles were full. The optic discs and fundi were normal. There was some facial weakness, especially weakness in retraction of the angles of the mouth. There was also some degree of stiffness of the neck and head retraction. He was unable to sit up. His arms were moved equally well, but there was very little movement of the legs which were hypotonic but not wasted. The deep reflexes were all much diminished or absent. The plantars gave a doubtful extensor

response. The abdominal reflexes were present. Sensation appeared to be normal. A tentative diagnosis of the Werdnig-Hoffmann form of progressive spinal muscular atrophy was made at first, but the spina bifida occulta raised the possibility that the case was one of the Arnold-Chiari malformation and on November 28 Mr. Northfield was asked to see the patient with this in view. He found that the child now used his hands with poor control and the legs were wasted and weak. A lumbar puncture was performed and gave fluid with 150 mg. protein per 100 ml. The ventricular fluid obtained at the same time contained the normal percentage of protein (10 mg. per 100 ml.). No excess of cells was found in either specimen.

On December 11, a subtentorial decompression operation was carried out to exclude the possibility of Arnold-Chiari malformation or tumour in the posterior fossa. No abnormality was discovered. The child died on the next day with hyperthermia to 105° F., and a very rapid pulse. He was then aged 3 years and 1 month.

A post-mortem examination was made nine hours after death. The head was large, and the skull was thin, but not abnormally so for the age of the child.

The brain weighed 1,400 grammes and was firmer than normal. It was normally convoluted. On section the white matter did not appear grey and except for the undue firmness it would easily have been passed as normal.

Microscopical examination of the brain.—Sections were made from various parts of the brain-stem and cerebellum for the most part by celloidin embedding of unmordanted pieces. Some large blocks were also put through the Kultschitsky-Pal process, and frozen sections were also made of representative areas for a study of the neurofibrils and the condition of the myelin.

Sections were also made from the cervical and lumbo-sacral enlargements and the mid-thoracic level of the spinal cord.

In sections stained for myelin the white matter of the hemispheres as a whole stained faintly, and microscopically showed numerous fine fibres, many with swellings on their course, a few coarser fibres with an irregular contour, and numerous darkly staining granules which appeared to lie free.

The *optic radiations* stood out as more darkly stained than the surrounding white matter throughout their course through the temporal and occipital lobes, and microscopically were more normal, but in them also there were many fine darkly staining granules and large globules with a pale centre and a more darkly stained capsular zone (fig. 4).

In the *cortex* there was a fair number of fine fibres, but in addition a deposit of fine granules often in aggregations and varying greatly in number from one part to another. Larger globular or irregular swellings lay on the course or at the termination of some of the myelinated fibres. Some darkly stained irregular myelin sheaths had collections of fine granules on their surface. There were also many aggregations of darkly staining granules in the walls of the cortical vessels. In the line of Gennari in the calcarine cortex there were many fine, darkly staining granules, but very few myelinated fibres were seen here.

The splenium of the corpus callosum showed an unusually large number of fine granules with comparatively few fibres many of which had irregular contours or globular swellings on their course (fig. 3).

In the *internal capsule* and *crura cerebri* very few fibres could be seen running in the vertical plane, but fibres passing across in the horizontal plane between the basal ganglia were stained, as well as granules and smaller and larger globules of myelin-like material. In the myelinated network of the optic thalamus swellings on the course of the fibres were plentiful, and many fine darkly-staining granules were seen, but on the whole the thalamus was well myelinated as well as the bundles of fibres passing in the lenticular nuclei.

The *external capsule* also was fairly well myelinated with fine fibres, but also contained a considerable number of fine granules and a few larger globules.

The *optic tracts* stained well with occasional ballooning of myelin sheaths and sparse granules. The capsule of the corpora mammillaria was made up of myelinated fibres, with very beaded and ragged contours and very numerous, large, darkly-staining granules were seen here.

In the *mid-brain* and *pons* there was pallor of the pyramidal tracts and of the fronto- and temporo-pontine fibres. No such distinction between the staining of these was seen as in the two cases published in 1933. The transverse fibres of the pons going to the middle peduncle stained rather palely, many showed globular swellings and fine black granules were abundant among them. By contrast the mesial fillet, superior cerebellar peduncle and median longitudinal fasciculus were well stained and granules were scanty in the tegmental region generally.

In the *spinal cord* there was marked pallor of the pyramidal tracts, and few normally myelinated fibres could be seen in this area but many swollen sheaths and abundant fine black granules were present, both here and in the ventral horns.

In the *cerebellum* the white matter of the hemispheres showed a network of myelinated fibres which was normal except for the spaces caused by the granular masses (unstained by this method) which will be described later. Sparse granules were present as well as occasional globular swellings on the sheaths. The hilum of the dentate nucleus was almost normal.

In *celloidin sections* stained with *iron hæmatoxylin* and van Gieson's counterstain the centrum semi-ovale of the cerebral hemispheres showed everywhere a striking absence of interfascicular oligodendroglial cells. It thus appeared much poorer in nuclei than normal white matter, the only nuclei seen being the pale oval nuclei of astrocytes and those on the cells of the vessel walls, as well as occasional small nuclei of microglial cells. There was no rarification or vacuolation of the ground substance, which contained numerous granular masses, rounded or oval in shape and measuring 15 to 20 μ in diameter. They were slightly more hæmatoxophilic than the surrounding ground substance. In some a very pale, small rounded nucleus, suggesting a necrotic oligodendroglial nucleus was seen, but the majority contained no nucleus. Accumulations of these bodies were seen in the perivascular spaces. The astrocytes were scarcely more numerous than normal but occasional double nuclei were seen and the cell body of all was swollen, and gave rise to numerous fine fibres. Occasional typical early compound granular corpuscles with slightly hæmatoxophilic granules were seen round the larger vessels, but nowhere else.

Different parts of the white matter did not differ greatly in appearances except that in the corpus callosum there was a greater accumulation of the granular bodies near the vessels than elsewhere (fig. 5). In the subcortical zone the bodies tended to be smaller and less rounded than more deeply in the white matter, but there were no more oligodendroglial nuclei here than elsewhere in the white matter. A few vessels in the white matter showed a moderate excess of lymphocytes in their walls but no true cuffing was seen.

Celloidin sections stained by Mallory's phosphotungstic acid as well as frozen sections stained by Holzer's method showed considerable fibrous gliosis throughout the white matter.

The cortex showed no abnormality either with hæmatoxylin and van Gieson's stain or by Nissl's method and it contained oligodendroglial nuclei of normal appearance and apparently in normal numbers.

The *basal ganglia* showed no abnormality in the grey substance, but in the bundles of white fibres traversing the globus pallidus and entering the putamen there were numerous granular bodies and no oligodendroglial nuclei. Numerous neuroglial fibres were seen in and around these bundles and there was also diffuse gliosis of the thalamus as shown by Mallory's phosphotungstic acid hæmatoxylin.

In the cerebellar white matter there was as complete a loss of oligodendroglial nuclei as in the cerebral hemispheres and it was strewn with small, rather ill-

defined granular bodies. A slight degree of lymphocytic cuffing was seen in the walls of the small vessels. In the cortex the most obvious abnormality was the presence of numerous torpedoes in the granular layer. These were especially well shown by the Gros-Schultze technique. They were equally distributed between the vermis and the lateral lobes and the upper and lower halves of the cerebellum. Few foliæ were without at least one, as seen in sections cut in the sagittal plane. Many contained a dozen or more. The line of Purkinje cells showed occasional gaps, especially in folia where torpedoes were specially numerous, and isomorphic gliosis in the molecular layer was more definite in such areas than elsewhere.

In the white matter there was everywhere a fairly dense isomorphic gliosis.

Sections stained for axis cylinders (Da Fano-Bielschowsky on frozen sections and Gros-Schultze on celloidin sections) showed a fairly close-felt work of fine fibres in all the areas examined. The axons tended to be pushed aside by the larger granular bodies, which stained in the frozen sections a faint sepia, with innumerable very fine darker dots. Most of the axons had regular contours but an occasional thicker axon with a rough irregular outline was seen. Such axons were most numerous in the splenium of the corpus callosum where some larger isolated axonal swellings were also seen, but even here the majority of the axons appeared normal and there did not appear to be any definite loss of axons.

Staining Properties of the Granular Bodies

I. *Frozen sections.*—In frozen sections stained by Scharlach R with alum hæmatoxylin, the white matter stained diffusely of a terra-cotta colour, but the number of recognizable myelin sheaths diminished rapidly on passing inwards from the cortex, in which the radial fibres stained well. More deeply in the white matter there were many fine granules which stained the same colour as normal myelin sheaths and which appeared to be the same as those which stained black by the Kultschitsky-Pal technique. The larger granular bodies stained a lavender tint by this method. No red staining lipoid was seen except in the perivascular sheaths of the medium-sized vessels, where it was mixed with irregularly shaped anisotrophic crystals, some of which also stained brilliantly red with Scharlach R. The granular bodies contained fine granules with a similar degree of anisotropism to that of the intact myelin sheaths, but the greater part of the granules in them appeared to be isotrophic.

Frozen sections stained by toluidin blue passed rapidly through the stronger alcohols and mounted in cedar wood oil (mersol) or a neutral oil (microil) without a bath of xylol or benzol, showed metachromatic staining of all the granular bodies and of some free granules throughout the white matter of the cerebral and cerebellar hemispheres. In the latter they were concentrated round the nucleus dentatus and in this situation were more resistant to fat solvents, such as absolute alcohol, than elsewhere in the cerebellum. In addition the neurons of the nucleus dentatus and globus pallidus contained masses of purple isotropic metachromatic granules. In most of the affected neurons these granules filled more than half of the cell body but did not appear to distend or to deform it. By contrast the neurons of the putamen, thalamus and cerebral cortex and the Purkinje cells were quite free from metachromatic granules. Unfortunately the nucleus subthalamicus (Luys) was not examined.

Sections of cortex and subcortical white matter stained by the Smith-Dietrich technique for cerebrosides showed a few greyish granules, but for the most part nothing except myelin sheaths was stained by this method.

II. *In celloidin sections.*—(*a*) *Mayer's mucicarmine with alum hæmatoxylin and metanil yellow* (*Masson*) on celloidin sections stained the majority of the granular bodies. The staining appeared as fine red granules which either filled the body entirely, or were mixed with other granules which took the yellow counter-stain.

The granules in the cells round the vessels, which resembled compound granular corpuscles, also stained yellow rather than red. Granular bodies containing red granules could be traced throughout the cortico-pontine and cortico-spinal tracts. In the medulla the pyramids were the only areas to show red staining granular bodies, which were both numerous and fairly large in them, though smaller than in the white matter of the cerebral hemispheres. In the pyramidal tracts in the cord they were rather smaller and many had a shrunken irregularly-shaped nucleus in them. In the cerebellar white matter the small granular bodies did not stain deeply with mucicarmine, except in the capsule of the nucleus dentatus where they were larger. Within the hilum of the nucleus dentatus only small ill-defined bodies which did not stain red with mucicarmine were seen. The granules in the neurons of the nucleus dentatus took the yellow counter-stain.

(*b*) *Mallory's connective tissue stain and Heidenhain's Azan*: Both Mallory's original formula, after preliminary mordanting in 2 per cent iron alum, and his 1937 formula for connective tissue, were used on celloidin sections, which were also stained by Heidenhain's Azan method. Of these three methods the original Mallory method tended to emphasize the blue-staining granules, the newer method left these pale, but stained the acidophilic granules brightly, while with Azan a very beautiful differential staining was given so that both blue and red granules were seen in the same body. With all methods the bodies with blue-staining granules were much the more numerous, the bodies with red-staining granules being everywhere sparse, though in a few places several were seen in a high power field. The red-staining (acidophil) granules tended to be larger than the blue granules, and many were everywhere scattered loosely in the tissues especially in the subcortical zone, where also the granular bodies tended to contain acidophilic granules. These granules also stained deep purple with Mallory's phosphotungstic acid hæmatoxylin, which left unstained the granules which stained blue with Azan. These blue granules certainly included those which stained with mucicarmine and possibly others which did not stain differentially for mucus. Although there was a larger proportion of bodies with red-staining granules in the subcortical layer, they were not so predominant here as in the two previously described cases. Layers of bodies containing red granules and staining deeply with phosphotungstic acid hæmatoxylin were seen along the walls of the vessels in some places.

Case 2.—A girl (H. S.) aged 33 months was admitted to the National Hospital on January 1, 1947, under Dr. J. McArdle and died there on January 17, 1947. The history given by the mother was that she had been a normal baby up till the age of 2 years, except for a convergent squint which developed when she was 22 months old, but cleared up in six months following the wearing of spectacles.

She had never jumped about in the perambulator like a normal baby. At the age of 2 years she was able to walk alone although she always tottered slightly in walking. In April 1946 at the age of 2 years she seemed to stagger in walking and to fall unexpectedly. She walked with her feet wide apart and avoided climbing stairs. From this time she regressed steadily. In July her right hand became jerky and clumsy and the left arm was similarly affected soon after the right. There were no signs suggesting headaches and the head had not increased notably in size. Since August she had been unable to walk alone and by Christmas she was unable to stand or to feed herself. She vomited twice at Christmas time. At the age of 2 she was talking and appeared to be quite intelligent but latterly she had not talked as much as before and her speech had been slower, deeper and rather slurred.

The patient was the youngest of four sisters, the older girls aged 15, 11 and 9 in January 1947 were quite normal and well. The mother was then 45 and the father 46, both were well.

On examination in hospital the child appeared healthy and well nourished. There was no enlargement of the skull. There was gross ataxia affecting the head

and arms as well as the legs. The speech was dysarthric with a trembling, hesitant quality. There was no evident loss of vision, no nystagmus nor any abnormality in the functions of the cranial nerves apart from the changes in speech already described. The optic discs were rather pale but appeared to be within normal colour limits. The legs were held rather rigid; the arms were flaccid and hypotonic. The tendon reflexes could not be obtained, and the abdominal reflexes were also absent. The plantar reflexes were both extensor in type. No sensory loss was made out. The gait was grossly ataxic, indeed the child made no attempt to move her legs normally and was quite unable to stand.

A lumbar puncture was performed on January 7 and fluid was obtained under a pressure of 110 mm. It contained 1 lymphocyte per c.mm. and a greatly increased protein (0·12 per cent). The Lange curve was normal and the Wassermann reaction negative. She was seen by Sir Charles Symonds on January 10 and considered by him to be a case of cerebral and cerebellar degeneration, but he recommended that a ventriculography should be done to exclude cerebellar neoplasm, and this was performed on January 16. The ventricular fluid contained 2 lymphocytes per c.mm. and 60 mg. per cent protein. X-rays of the ventricles showed no distension or displacement. On the following day there was a rise of temperature to 104° and the pulse became uncountable and she died about thirty-six hours after the ventriculography.

The post-mortem examination was delayed till sixty hours after death, but the weather was cold at the time and the body was kept in the refrigerator, so that there was little post-mortem decomposition. The body was well nourished and there was a fresh right parietal burr hole for ventriculography. The skull was of normal thickness, the convolutions not flattened and there was no herniation into the incisura tentorii or foramen magnum. The cerebellum was of normal size but the inferior vermis was rather more exposed than normal. The pons appeared rather small. No disease of the vessels at the base of the brain was present. The brain was rather firmer than normal, and when the right frontal and occipital poles were cut off they kept their shape better than is normal at this age. The spinal cord was also removed; it showed no naked-eye abnormality.

The body cavity showed little evidence of disease. The thymus extended down over the upper two-thirds of the pericardium. There was slight superficial collapse towards the bases of both lungs but no evidence of bronchopneumonia. The heart and other organs were quite healthy.

Frozen sections of the *kidney* stained by toluidin blue showed metachromatic, rather brightly anisotropic material in the epithelial cells of the looped tubules of Henle. It stained a dull lilac colour in sections stained Scharlach R and Ehrlich's hæmatoxylin. It disappeared when the sections were placed overnight in chloroform and almost entirely in those treated with ether before staining, and therefore appeared to be of lipoid character.

In the *liver* there was slight fatty degeneration of the parenchymal cells of the lobules and some brightly sudanophilic lipoid were also seen in the portal spaces, in which were also seen histiocytes containing similar metachromatic material to that seen in the kidneys. The dull lilac colour of this in sections stained with Scharlach R and Ehrlich's hæmatoxylin contrasted with the brightly sudanophilic lipoid in the neighbourhood. It disappeared from frozen sections treated with xylol and almost entirely from those treated with ether before staining.

The *brain* was further sectioned after fixation in formol saline solution, but no evident disease was seen either in the grey or white matter on naked-eye inspection.

Large celloidin sections were made of representative areas of the cerebral and cerebellar hemispheres and horizontal sections of the brain-stem and cord were also cut after celloidin embedding. Frozen sections of various areas of the brain were also made and stained by the Holzer and Bielschowsky techniques and by toluidin blue and Scharlach R with hæmatoxylin. The appearances found in all

these sections were so similar to those already described in Case 1 that only points of divergence or those requiring special emphasis will be described.

In large Weigert-Pal (Kultschitsky-Pal) sections of the cerebral hemispheres there was a diffuse demyelination which included the subcortical arcuate fibres, but spared to some extent the optic radiations which formed a sharply defined darker band in sections of the temporal and occipital lobes (fig. 2). Throughout the demyelinated areas were scattered fibres, many of which were irregularly beaded, and a diffuse sprinkling of fine black granules. In sections of similar areas stained by Loyez' method for myelin sheaths there was, to the naked eye, much darker staining of the white matter but under the microscope there were few normal myelin sheaths; rather there was a diffuse granular detritus with occasional irregularly swollen myelin sheaths running through it.

In sections stained by Loyez' method for myelin the lower and posterior parts of the cerebellar hemispheres (cut in parasagittal section) stained less darkly than the upper and anterior parts. No difference of this kind was seen in the white matter of the vermis.

Granular bodies similar to those in Case 1 were found in great profusion throughout the demyelinated areas. In sections stained by iron hæmatoxylin and van Gieson it was seen that many, but by no means all or even perhaps the majority, had an irregularly shaped small darkly staining nucleus often peripherally placed in them. Occasionally two nuclei are seen in one of these bodies. There was a practically complete absence of oligodendroglial nuclei not only in the white matter of the cerebral hemispheres, including the sheaves of fibres passing into the caudate and lenticular nuclei, but also in the ventral part of the brain-stem where granular bodies were present among the cortico-pontine and cortico-spinal fibres. Even in the superior cerebellar peduncles, which were fairly well myelinated, there appeared to be loss of oligodendroglial nuclei and some granular bodies. The white matter of the cerebellar hemispheres and vermis was similarly affected. The cortex appeared to be normal. There was also great diminution in the number of oligodendroglial nuclei in the white columns of the cord. As in Case 1 there appeared to be no loss of oligodendroglia in the cerebral cortex or the grey matter of the basal ganglia.

Holzer stained sections of the white matter showed everywhere considerable overgrowth of neuroglial fibres. There were throughout the white matter many swollen bodied astrocytes some of which contained marginal granules which stained red with Azan, and terra-cotta with Scharlach R.

Staining Reactions of Granular Bodies

I. *Frozen sections.*—With Scharlach R and hæmatoxylin the granular bodies stained a dull lilac colour, except in the sheaths of a few of the larger vessels where they stained orange or red. Mixed with this sudanophil lipid were anisotropic crystals which remained colourless and appeared to consist chiefly of cholesterol. With Nile blue sulphate the granular bodies stained pink and with toluidin blue on frozen sections they also stained pink metachromatically. With this stain, as well as with Scharlach R, many of the granules were faintly anisotropic, but less so than the normal myelin sheaths in the neighbourhood. Many of the lipochrome granules in the neurons of the nucleus dentatus also stained metachromatically with toluidin blue, but that in the cortical neurons failed to do so (figs. 9, 10, 11). In celloidin sections neither metachromasia nor anisotropism was apparent.

II. *Celloidin sections.*—Many of the granular bodies stained darkly by Loyez' myelin stain in celloidin sections. With mucicarmine they stained rather variably, many contained a certain number of red-staining granules and in some all the granules stained red. The reaction appeared to vary from one area to another. For example in the pyramidal tracts in the medulla and in the ventral half of the

pons and mid-brain all the granular bodies stained red. With Azan in celloidin sections the granules in the bodies stained either red or blue, as in Case 1, the bodies containing red granules preponderating towards the cortex and those containing blue granules more deeply in the white matter, but many bodies contained granules of both colours. The fine granules on the margin of the swollen cytoplasm of the astrocytes were more often red than blue. The Foot-Masson trichromic method gave a similar result. As in Case 1 only the granular bodies containing acidophilic granules stained darkly by phosphotungstic acid hæmatoxylin.

Case 3.—M. C., a girl of 2 years and 9 months, died in the Westminster Hospital on October 1, 1947, and we are very grateful to Professor R. J. V. Pulvertaft and Dr. A. D. Morgan for sending us material and clinical records from this case.

The child was born on January 5, 1945, and progressed normally till she was a year old. She sat up at 7 months and was able to walk at 11 months. Between 9 and 12 months of age she had whooping-cough and this hung on for eight or nine months. When 15 months old her mother noticed that she was not progressing normally, as she could no longer sit up or stand or walk about. She was also getting convulsions about four or five times a month. They began by the child holding its breath; it then got blue and the convulsion followed at once. According to the mother the child's speech and intelligence seemed to be unimpaired. The child had developed chicken-pox in June 1947 and still had the scabs of this when she entered hospital. The father and mother were both healthy.

She was admitted to the Westminster Hospital on July 15, 1947. She then appeared to be mentally backward. The knee and ankle jerks were absent, the plantar reflexes of flexor type. On August 3 she was noted to be losing weight and was listless and lethargic. There was incontinence of fæces. The head measured 18½ inches. She could not sit up, but held her head up. The upper limbs were rigid, the knee-jerks normal and plantar reflexes flexor. By September 17 she had to be fed through an œsophageal tube. She then had a vacant stare and a feeble cry. The pupils reacted sluggishly to light and accommodation. There was bilateral ptosis with a right-sided internal strabismus, and doubtful nystagmus on looking to the left. The fundi were normal, except that the left optic disc appeared pale. The soft palate appeared to be weak. All four limbs were now rigid and no deep reflexes could be elicited. The plantar reflexes were still flexor. Dr. S. P. Meadows saw the child and made a diagnosis of demyelinating cerebral sclerosis. The cerebrospinal fluid was examined on September 12. It was colourless and clear but formed a spontaneous coagulum. It contained 3 lymphocytes and 0·20 per cent protein with positive globulin tests. The Lange curve was normal.

A post-mortem examination was made on October 3. The body was dehydrated. The skull was normal and the brain was of normal size and showed no evidence of increased intracranial pressure. The white matter generally appeared rather congested but otherwise normal. No naked-eye abnormality was discovered in the cortex, brain-stem or spinal cord either externally or on section.

In the right lung a calcified Ghon lesion was found in the upper lobe, just under the pleura, and there was also caseation of the related mediastinal glands. Patches of bronchopneumonia were seen in the lower lobes of both lungs. The other bodily organs appeared healthy.

Portions of the cerebral hemispheres, unfortunately not including the occipital lobe, and of the brain-stem, cerebellum and spinal cord were sent to one of us (J. G. G.) after fixation in formol saline. From these sections were made both after celloidin embedding and by the freezing technique. They showed a condition essentially similar to that found in the other two cases.

The Kultschitsky-Pal method was used on the spinal cord, pons, cerebellum and parts of the frontal lobes. In the *cord* it showed pallor of both the crossed and direct pyramidal tracts. In the *pons* the descending tracts in the ventral half

contained some small myelinated fibres with many larger irregularly swollen myelin sheaths among them and many small darkly staining granules. The more mesial bundles (fronto-pontine) appeared to be almost cleared of myelin. The other fibre systems including the transverse fibres of the ventral half appeared normal. The Loyez method for myelin was used for the other pieces embedded in celloidin. It showed in the *medulla* a few fine normal fibres in the pyramids, with many swollen bubbles of myelin and numerous small granules. The fibres of the mesial fillet stained well as did also the more dorsally placed fibre systems. The intra-olivary fibres stained less well, but were more normal than those in the pyramids. In the *cerebellar* white matter there were many normal fibres but also many ballooned fibres and black-staining granules. By the Kultschitsky-Pal technique the lower and dorsal half including the white matter of the amygdalæ stained very palely.

The *optic nerves* and *chiasma* were well myelinated but here also some ballooning of myelin sheaths was seen.

Sections in the coronal plane through four levels of the *basal ganglia*, through the *cortex* and *white matter* towards the vertex in the *precentral* region and through the inferior part of the *temporal lobe* were embedded in celloidin without mordanting, and a section through the anterior end of the *corpus striatum* was treated by the Kultschitsky-Pal technique. By the latter stain the white matter everywhere stained palely, but more darkly in the corpus callosum, and on examination with higher magnifications showed both thin fibres, thicker ballooned sheaths and fine black-staining granules. With the Loyez stain the white matter stained more darkly but the microscopical appearances were similar. In addition numerous granular bodies were seen throughout it, many of them containing granules which stained black by this method (fig. 7).

Sections stained by iron hæmatoxylin with van Gieson showed a very similar picture to that seen in the other cases. In the *cord* there was more loss of oligodendroglial nuclei throughout the white columns with an increase of small chiefly irregularly shaped nuclei in a narrow zone under the pia mater. A few of these were rounded and may have been oligodendroglial in nature but the majority were clearly microglial. No abnormal products were seen by this method in the ventrolateral columns but with the Azan stain occasional blue-stained bodies were seen here. In the dorsal columns at the cervical level there were some masses which stained brownish with hæmatoxylin-van Gieson, violet with Azan and lavender with phosphotungstic acid hæmatoxylin. Diffuse neuroglial sclerosis was present in both dorsal columns and pyramidal tracts.

In the *medulla* there was a loss of oligodendroglial nuclei throughout and as in the cord a cellular zone under the pia mater. The amount of oligodendroglial degeneration present may be gauged from the fact that only five nuclei of this character were seen in the total transverse area of the tractus solitarius. The hilum of the olive was similarly poor in oligodendroglial nuclei. There was an area of rather loose texture between the pyramid and the olive on both sides in the position taken up by the ventral cavity in syringobulbia. There were here rather more neuroglial fibres than elsewhere in the pyramids, which showed a slight diffuse gliosis. With the Azan stain blue and blue-red granular bodies were seen throughout the medulla, even in the otherwise normal mesial fillet. They were rather more numerous in the pyramids than elsewhere, but were present also throughout the dorsal part except in the subventricular grey matter.

In the *pons* the loss of oligodendroglial nuclei was most evident in the ventral half, both in vertically and horizontally coursing fibre systems. There were many swollen astrocytes among the vertical fibres. There appeared to be some degeneration of the neurons of the nuclei pontis, many of which contained cytoplasmic granules which stained purple with phosphotungstic acid hæmatoxylin. All the ventral half was packed with granular bodies most of which stained blue with Azan, but some contained red granules or granules of both colours. In the fillet

also a few blue-staining granular bodies were seen. In the superior peduncle there were few and these mostly contained red granules. The median longitudinal fasciculus also contained a few blue-staining granular bodies. There was much less fibrous gliosis in the tegmentum than in the ventral half.

In the *optic nerves* and *tracts* also granular bodies were seen, especially in the tracts, less in the chiasma and very few indeed in the septate part of the optic nerves. Most of these bodies took a blue stain with Azan.

In the *cerebellar white matter* also there were many granular bodies most of which contained blue granules, but many also contained red granules or granules of both colours. There was no evidence of gliosis in the cerebellum and there was no difference either in this or in the number or type of granular bodies present between the vermis and lateral lobes.

Throughout the *white matter* of the *cerebral hemispheres* including the internal and external capsules there were very numerous granular bodies staining blue, red or both with Azan. Swollen-bodied astrocytes, mostly mononucleated but some with two or more eccentric nuclei, and containing a few red-staining granules near the margin were also seen by this method. The disappearance of oligodendroglial nuclei was as evident throughout the white matter as in the other cases, but an occasional small round nucleus was seen in the white matter, some staining grey with iron hæmatoxylin and evidently undergoing necrosis. The relation of nuclei to the granular bodies varied. Most had none, and where a nucleus overlay a granular body the juxtaposition appeared most often to be fortuitous.

In frozen sections the Holzer technique showed a diffuse fibrous gliosis with a condensation round the vessels and an occasional swollen astrocyte giving rise to thicker fibres.

By the Bielschowsky technique, the cortex appeared normal, but the white matttr became progressively impoverished of axons on leaving the cortex and passing more deeply. Most of the remaining fibres were thin but some were irregularly thickened.

In sections stained by Scharlach R, with alum hæmatoxylin, the bodies stained from mauve to brick red, but very few of the latter type were seen. No bright red-staining lipoid was seen except in the bodies of fat granule cells in the perivascular spaces where they were mixed with unstained acicular crystals. Both these and some of the red-staining globules were anisotropic. Some of the granules in the granular bodies, which did not stain more than a terra-cotta colour with Scharlach R, were also anisotropic.

In frozen sections stained by toluidin blue and mounted out of alcohol in cedar wood oil or "microil" many of the granular bodies, both in the cerebral and cerebellar white matter, took a bright pink metachromatic stain and were also anisotropic with this technique, but the doubly refracted light appeared of a pale greenish colour, and the appearance of anisotropism may have been due to some substance in the bodies which did not take the metachromatic stain. The anisotropism of the granular bodies was much more definite in this case than in the two others here reported. As in the other cases the granules, which stained red with Azan, stained purple with phosphotungstic acid hæmatoxylin and appeared to be those which took a black colour with Loyez' method.

The cortex as in the other cases appeared quite normal and contained its usual quota of oligodendroglial nuclei. A smaller proportion of the cytoplasmic granules in the nucleus dentatus stained metachromatically in this case than in Case 2.

Case 4.—B. L. (female), born on May 3, 1946, was admitted to the National Hospital on November 24, 1948, under the care of Dr. J. St. C. Elkington and died there on February 11, 1949, at the age of 2 years and 9 months.

She was the first child of healthy parents, born after a normal labour. She first sat up at 6 months of age and between 10 and 12 months became able to pull

herself up on to her feet. Four weeks later she could walk by holding on to furniture. But in spite of this early start she never became able to walk alone although up to July 1948, when she was 2 years and 2 months old, she could walk pushing a perambulator. When 14 months old she could say "Mummy" and "Daddy" and progressed well with talking until July 1948, in fact she seemed brighter in this respect than a cousin of the same age. She knew her own dolls by name, and was clean in her habits.

At about the age of 12 months she had a series of bilious attacks with vomiting. She received several minor head injuries, owing to the tendency to fall. At 5 months of age she had fallen on her side, at 10 months she fell out of her cot and soon after this she fell out of a tub. None of these injuries was serious.

In May 1948, when 2 years old, she developed an external squint, and about the same time became constipated and had little appetite.

In July 1948 she was hit on the head by a door, but did not lose consciousness. Since this injury her mental and bodily powers had regressed rapidly. Seven weeks before admission she frequently put her head on her right shoulder and remained in this position for a long time. The doctor who was called in considered that during these periods she was semiconscious. Otherwise there were no fits. She had also become "wet and dirty."

On examination at the National Hospital she was found to be a pale, puffy-faced, thin child, who lay quietly or cried if upset, but did not talk. She would follow a light with her eyes or look towards a noise, but did not use the arms or legs purposefully. The optic discs were pale, but did not suggest blindness to the ophthalmologist who examined them (Mr. Keith Lyle). The pupils were dilated and fixed, the right being larger than the left. There was a jelly-like nystagmus, synchronous in the two eyes on looking straight ahead, laterally or downwards. She did not look upwards though the eyelids moved up slightly when a noise was made above her head. She appeared to hear quite well. When left alone the arms were kept in a position of internal rotation at the shoulders and pronation at the elbows, with flexion of the fingers. The right arm was more flexed than the left, which was sometimes extended. There was moderate rigidity of all muscle groups which varied from time to time but was not altered by movements of the head. There was equal and fair power in the two arms. Bilateral grasp reflex was present, and when the object grasped slipped from the child's hand there was sometimes a rebound phenomenon on the right side, but not on the left. She could not sit up, but could move herself about in bed. The legs were usually kept in rigid extension; the left leg rarely relaxed from this position; the right leg was less rigid but could be made more so by turning the head to the right. Power was feeble in both legs and there seemed to be little attempt at co-ordination. No tendon-jerks could be obtained from the arms, but the knee and ankle jerks were present. The abdominal reflexes were absent and the plantars extensor in type. She appeared to dislike pin-prick everywhere equally, but sensation could not otherwise be tested.

By December 9 the child had ceased to react to sights and sounds. On December 13 and 14 there was slight pyrexia and head retraction was noted. A lumbar puncture done at this time gave slightly blood-stained C.S. fluid (2,000 red blood cells per c.mm.) under normal pressure. It contained 2 lymphocytes per c.mm. and 100 mg. protein per 100 ml.

By December 22 she had to be tube fed and she remained in this condition of complete dementia until her death on February 11, 1949.

A post-mortem examination was made by Dr. W. Blackwood after a delay of about sixty hours, formalin having been injected into the cisterns at the base of the brain after twenty hours. The weather was cold and the body was in a good state of preservation. The only abnormality in the organs of the thoracico-abdominal cavity was that the gall-bladder was small with a pale, thick wall and its contents were almost colourless. No calculi were found in it or in the bile ducts.

The brain, spinal cord and meninges showed no abnormality on naked-eye examination.

After fixation the brain weighed 928 grammes, the cerebellum and brain-stem weighing 95 grammes. The cerebellar hemispheres appeared shrunken and the cerebellar folia more prominent than normal, standing up as firm rounded ridges on the surface. The white matter of the cerebellar hemispheres was firm.

On section of the cerebral hemispheres the centrum ovale was very white and unduly firm. In the zone of the deepest layers of the cortex there was a fine external pale layer and a thin brownish layer underneath this, the two layers being about 1 mm. in thickness when taken together.

There was a rather narrow, grey line in the position of the external capsule, and the internal capsule also appeared rather greyish and shrunken, but apart from these two areas there was no discoloration of the white matter. The brain-stem appeared normal on section.

The microscopical appearances in this case were very similar to those in the other three cases, but there was rather more demyelination and a more complete disappearance of oligodendroglial nuclei, even from many areas which had not undergone demyelination. In sections from various parts of the cerebral hemispheres the appearances were almost identical, and it is therefore only necessary to indicate where variations occurred.

With nuclear stains (iron alum hæmatoxylin-van Gieson, Nissl, etc.) there was a practically complete loss of oligodendroglial nuclei, which affected not only the white matter, but also the deeper layers of the cortex (fourth to sixth) and the basal ganglia. In the third cortical layer there was only a relative loss and superficial to this no disappearance of oligodendroglial nuclei was evident. Granular bodies of similar nature to those seen in the other cases were present in large numbers throughout the white matter. As in the other cases those containing granules which stained red with the Azan method were more numerous near the cortex, whereas those with blue-staining granules preponderated at all deeper levels. Many bodies contained both blue and red granules. The perivascular sheaths of many of the small vessels were distended with bodies which took the blue stain. These bodies were well stained in celloidin sections, but in paraffin sections took the dye very poorly. As in the other cases the great majority appeared to have no nuclei. No metachromasia was seen in celloidin sections stained by toluidin blue and passed through xylol to cedar wood oil, as in the ordinary Nissl technique; but if xylol was avoided, and the sections transferred directly from 95 per cent alcohol to "microil" (a mixture of castor oil and synthetic resins) all the granular bodies, which took a blue colour with Azan, stained metachromatically, and in this mountant the pink colour lasted for many weeks. As in the other cases the granules which stained blue with Azan, stained pink or red with mucicarmine, and the Azan-red granules stained with Mallory's phosphotungstic acid hæmatoxylin, and with Loyez' iron alum hæmatoxylin. The Hotchkiss-Schiff periodic acid-fuchsin technique, applied to celloidin sections of this case, gave a beautiful differential staining of all the granular bodies, including those in the Virchow-Robin spaces (fig. 6). Frozen sections stained with Sudan IV showed no scarlet lipoid except in the walls of a few vessels. The granular bodies stained a terra-cotta colour similar to that of the remaining myelin sheaths, or took the hæmatoxylin counter-stain rather more strongly. With Sudan black, the bodies took a variable dirty brown stain. The Baker modification of the Smith-Dietrich technique for phospholipids stained the myelin sheaths and many of the small scattered granules lying between them (which also stained by Loyez' method for myelin) but almost all the granular bodies remained unstained, only an occasional blue granule being seen lying in or on a granular body. In spite of the absence of oligodendroglial nuclei from the cortex and basal ganglia, granular bodies were not seen there, except in relation to the heavier bundles of nerve fibres.

Throughout the white matter all the astrocytes had swollen cytoplasm and had formed numerous fibres, so that there was a diffuse fibrous gliosis. With Azan and Mallory's phosphotungstic acid hæmatoxylin many showed granules (Azan red) in the periphery of their cytoplasm. Nowhere in the white matter were the astrocytes as numerous as the granular bodies. No gliosis was seen in the cortex or basal ganglia. In the thalamus there was a considerable variation from one area to another in the proportion of Azan-red and Azan-blue granules. Metachromatic bodies were here abundant, more so than in the putamen.

Large Kultschitsky-Pal sections were made through the entire coronal plane of the hemisphere, in the frontal and occipital regions. The latter showed relative sparing of the optic radiations, but more demyelination of these than in the other cases. Some sparing of myelin was also seen in the pre- and post-central convolutions. Elsewhere there was extreme pallor, and under the microscope only isolated myelin sheaths with numerous fine black-staining granules were seen throughout the white matter. In the frontal section the anterior end of the fornix, here closely applied to the under surface of the corpus callosum, remained well myelinated, and the myelinization of the olfactory tract also appeared to be normal, or almost so. A few granular bodies near the cortex stained rather faintly by this method, but none elsewhere.

The *optic nerves* were as fully cleared of oligodendroglial nuclei as other areas of white matter; there was an excess of microglial nuclei under the pial investment. Granular bodies were seen at the level of the optic chiasma, but not anterior to this. There was considerable loss of nerve fibres and an apparently greater loss of myelin sheaths, with many fine granules stainable by Loyez' method.

In the *mid-brain* and *pons* no oligodendroglial nuclei were seen ventral to the aqueduct and fourth ventricle, but in the superior medullary velum there were numerous rounded nuclei, rather larger than the normal oligodendroglial nuclei. There was a considerable diffuse fibrous gliosis throughout the brain-stem, especially in the region of the fronto-pontine and cortico-spinal tracts. Mucicarmine and Azan-blue-staining granular bodies were abundant in these ventral areas, whereas many containing Azan-red or both blue and red granules were seen in the tegmentum.

In the *medulla* also the pyramidal tracts were the seat of heavy gliosis, and contained many Azan-blue granular bodies, and granular bodies of more mixed character were present throughout the retro-olivary part of the medulla.

The pyramidal tracts throughout the cord presented the same appearance, i.e. loss of the fibres, heavy gliosis and the presence of granular bodies containing Azan-blue granules. A few such bodies were also present in the columns of Goll where the myelinated fibres were more sparse than normal. Elsewhere in the cord no definite alteration was seen except a global loss of oligodendroglial nuclei. It was doubtful whether any such cells were present. There appeared to be an excess of microglia in the layer immediately under the pia-mater (fig. 8).

Kultschitsky-Pal staining of the brain-stem showed pallor of the crus, especially of its mesial and lateral thirds (fronto- and temporo-pontine fibres). The superior cerebellar peduncles, fillets, median longitudinal fasciculus and the roots of the cranial nerves stained well. The central tegmental tract was rather pale. The transverse fibres of the pons and the restiform body also stained normally. The pyramidal tracts in the medulla and spinal cord were pale, and under higher microscopical powers were seen to contain sparse myelin sheaths, many of them irregularly swollen, and numerous small darkly stained granules.

The *cerebellum* with the Kutschitsky-Pal technique stained much more deeply than the cerebral hemispheres, but there was relative pallor of the lower and posterior parts in parasagittal sections of the hemispheres. By this method and by Loyez' stain, the myelin sheaths in the hilum of the nucleus dentatus stained well. Elsewhere there was an admixture of myelin sheaths and grey-staining granules. A

number of larger granular masses, corresponding to those staining red with Azan, was also seen external to the nucleus dentatus.

With cell stains there was no obvious shrinkage of the cortex or loss of granules or Purkinje cells. There was, however, a diffuse isomorphous gliosis throughout, with an increase in the number of Bergmann cells which formed a very prominent layer. Elsewhere there was a moderate excess of astrocytes, but less swelling of the cell bodies than in the cerebral hemispheres; many of them contained a few fine Azan-red granules. Granular bodies were abundant, though less numerous than in the cerebral hemispheres, the greatest number being concentrated round the nucleus dentatus, while the hilum of this nucleus was relatively free from them. Both Azan-blue and Azan-red granular bodies were seen, as well as many which contained granules of both kinds.

In frozen sections the neurons of the nucleus dentatus contained a collection of rather indefinitely granular material at the base of the cell, staining metachromatically with toluidin blue. It was difficult to be certain whether this was the same material as gave a fairly bright stain with Sudan IV, that is whether it was identical with lipochrome, but the latter granules appeared to be more diffusely spread in the cytoplasm than those which stained metachromatically. They also stained by the Schiff-Hotchkiss method, which normally stains lipochrome. In celloidin sections and in frozen sections left overnight in absolute alcohol no metachromatic staining was obtained. With the Schiff-Hotchkiss technique under these conditions the granules took a fainter pink colour. They remained, as normally, unstained in the iron hæmatoxylin, van Gieson, Nissl and Azan techniques, but rather fine granules were stained by Mallory's phosphotungstic acid hæmatoxylin.

The nerve roots of the cauda equina stained fairly well by the Kultschitsky-Pal technique, but here also, especially in the ventral roots, there were numerous black granules, either lying irregularly between the myelin sheaths, or collected into large fusiform masses measuring about 80 $\mu \times 12 \mu$. In frozen sections stained by toluidin blue, the material in these masses stained a purplish metachromatic colour, not quite so red as the π granules in the cells of Schwann. The latter were quite brightly anisotropic and a few rather faintly anisotropic granules lay in the fusiform masses. The larger metachromatic granules corresponded in size and arrangement to those stained by the Kultschitsky-Pal technique.

In frozen sections of the *liver,* material which stained metachromatically with toluidin blue was seen collected in phagocytes in the portal spaces of the liver (figs. 12, 13). The number of these phagocytic cells varied from one area to another, but usually three or four were present, often at one side only of the portal vein. Fine granules which stained similarly were also seen in many of the neighbouring liver cells. The Schiff-Hotchkiss technique also stained the granules both in the liver cells and in the phagocytic cells in the portal spaces, and in addition many Kupffer cells which lay near the outer margin of the lobules. Similar but less abundant staining was obtained in a case of amaurotic family idiocy fatal at the age of 4 years (Bird, 1948, Case 2) but no metachromatic staining was obtained here. The metachromatic material in the liver appeared to be isotropic. It was not seen in sections left in absolute alcohol overnight, though this treatment had little or no effect on the material staining with the Schiff-Hotchkiss technique.

In the *kidneys,* as in the other cases, the epithelium of the tubules of Henle (apparently the ascending limb) was filled, in frozen sections, with metachromatic granules (figs. 14, 15). In sections stained by Sudan IV these granules did not stain, but both with this stain and with toluidin blue in sections mounted in "microil" out of 95 per cent alcohol, abundant brightly anisotropic granules were seen in the epithelium of these tubules. The transmitted light was in both cases white, and it is therefore probable that the anisotropism was due to granular material of some kind other than that giving the metachromatic stain. Neither metachromatic staining nor anisotropism was seen when the sections were left in

absolute alchohol overnight. Sections of the kidneys of the case of amaurotic family idiocy and of a case of subacute inclusion body encephalitis in a child of 9 years showed no metachromasia when stained by the same method. Both in these controls and in the case under discussion the Schiff-Hotchkiss technique stained a row of granules near the free margin of the convoluted tubules, and a few tube casts, but did not stain the looped tubules of Henle, which also remained unstained by the Baker modification of the Smith-Dietrich technique.

The *suprarenal* cortex had its usual complement of sudanophil lipoid, but this did not give any metachromasia.

Discussion

Clinical.—These four cases thus present a clinico-pathological picture which closely resembles that in two children described by one of us (Greenfield, 1933) but differs from that in all other cases of diffuse cerebral sclerosis which have been described up to date. In this group of six cases the clinical history is similar. The children have appeared to progress normally up to the age of 1 or 2 years; there is then a progressive failure in walking and arm movements without at first any evident diminution of intelligence or loss of sight or hearing. The histories obtained suggest that along with weakness of the limbs there was from the first considerable ataxia and this was obvious in all the children at the time of their admission to hospital. Eventually there was little attempt to move the limbs which were held rigid or lay flaccid. The deep reflexes were not obtained from the arms in any case, and the knee and ankle jerks were also unobtainable, at least in the earlier stages of the illness, in all but one of the cases. While it may normally be difficut to obtain the arm-jerks in children of this age, the disappearance of the knee-jerks and ankle-jerks in children whose legs were kept rigidly extended (*v.* Cases 2 and 3) is not easily explained.

Loss of vision was present for three months before death in one of the cases reported in 1933 but was not definitely observed in any case of the present series. In Case 4 there may eventually have been loss of vision and of hearing as the child took no notice of a light or of sounds, but there was by this time gross dementia. In Cases 2, 3 and 4 there was strabismus; in Cases 2 and 4 it was noticed by the parents at about the age of 2 years but apparently cleared up before admission to hospital. While some loss of balance in the eye muscles is not uncommon at this age in children with errors of refraction, the presence of strabismus in so large a proportion as half of this group of cases is remarkable. Ptosis was present in Cases 1 and 3 and nystagmus was well marked in Cases 1 and 4 and doubtfully present in Case 3. Inability to look upwards was noted in Case 4. The first evidence of the onset of dementia was loss of sphincter control which had appeared in Cases 1, 3 and 4 on their admission to hospital. In Cases 1 and 2 the story was abruptly ended at

this stage by surgical measures carried out to establish the diagnosis. In Case 3 the child eventually became obviously demented but less so than in diseases such as amaurotic family idiocy or subacute encephalitis in which the cerebral cortex is primarily involved. In Case 4, however, dementia was complete for the last month of life. In this case, as in the second of the 1933 cases, there were fits. The age at death was very similar in all these cases: 3 years and 1 month in Case 1, 2 years and 9 months in Cases 2, 3 and 4. This resembles very closely the age at death of the two cases recorded in 1933, which was about 3 years in both cases. But the variation in date of onset and progress of the disease is greater than would appear from the age at death, as in the eldest (Case 1) the disease was, both clinically and pathologically, at an earlier stage than in Case 4 in which death in complete dementia occurred at the age of 2 years and 9 months.

Another feature common to all these three cases was the high protein content of the cerebrospinal fluid which was between 0·10 per cent and 0·20 per cent. This also agrees with Case 2 (1933) in which it was estimated at 0·12 per cent. No lymphocytosis was present in any of these four cases and the Lange reaction was normal.

The large size of the brain in the two male cases (Case 2 (1933), 1,287 grammes, Case 1 of this series, 1,400 grammes) may be considered to be within the limits of normal, but it is interesting that an elder brother of the former patient was stated to have died at the age of 2 years and 10 months of a condition diagnosed as hydrocephalus. This is the only suggestion that the disease may be of a familial character. The other siblings of this patient were normal, as well as three siblings in Case 2 of the present series. In the other cases either the patient was the only child, or no family history was obtained. The evidence therefore, so far as it goes, is against the disease being familial.

In two of the patients the first symptoms were noticed to come on after one of the infectious diseases of childhood. Thus in Case 1 (1933) the first symptoms were noted at the age of 2 years after whooping cough, in Case 2 (1933) after measles and bronchitis which set back the child's progress so that he never walked. In Case 3 of the present series there was a history of an unusually prolonged attack of whooping cough coming on before the child was 1 year old. These illnesses may have little significance in the ætiology of the condition, and no history of such illness was obtained in either Case 1 or 2 of the present series. Indeed the history, as obtained from the parents, gives little evidence of any predisposing cause for the cerebral degeneration.

Differential diagnosis.—These features compose a fairly constant clinical picture which must be distinguished from other acquired diffuse cere-

bral disorders of childhood whether infective or degenerative. The insidious course of this variety of diffuse cerebral sclerosis at once excludes all the acute forms of encephalomyelitis both polioclastic and demyelinating. The course of subacute inclusion encephalitis (Brain, Greenfield and Russell, 1948) is also insidious, but has on the whole been shorter—nine weeks to six months—than that of the disorder now being described. It has been reported in older children, though there is probably no reason why it should not occur in a child of 3. In accordance with the cortical distribution of the lesion progressive dementia has been the presenting symptom, myoclonic jerks or other involuntary movements have been present in most cases and the cerebrospinal fluid has shown no excess of protein. Van Bogaert (1945) has described 3 cases of subacute sclerosing leuco-encephalitis and Rosanoff (1947) 2 similar cases. All these occurred in older children: van Bogaert's patients were aged 13, 14 and 5½, Rosanoff's 6 and 9. This disorder ran a subacute course terminating fatally in from three to six months. In contrast to our patients dementia was an early symptom, accompanied by aphasia, agnosia and apraxic manifestations, hyperkinesia and hemiballismus and clonic epilepsy. There were no characteristic changes in the cerebrospinal fluid, though in one of Rosanoff's cases there was a paretic colloidal gold curve.

Confusion with the various forms of cerebromacular degeneration is not very likely to arise, the onset of the infantile form occurring earlier and that of the juvenile form later than in our patients. Moreover the early onset of visual failure with the accompanying atrophic or pigmentary retinal changes and of mental deterioration distinguish the lipidoses from the form of progressive cerebral sclerosis reported here.

Krabbe (1916) described a familial form of diffuse brain sclerosis arising in infancy, at the age of 4 to 6 months, with crying followed by apathy or stupor, muscular rigidity and tonic seizures, and terminating fatally in about a year, but the earlier onset and longer course distinguish this condition from the one described in this paper.

Scholz (1925) described a similar disorder arising at the age of 8 or 10. The Pelizaeus-Merzbacher variety arises in infancy and runs a much more chronic course lasting for many years. It is also familial. In typical cases of Schilder's disease the early onset of cortical blindness and deafness, the frequent occurrence of ophthalmoscopic changes in the optic discs and the slower course are distinguishing features, but an atypical sporadic case of Schilder's disease beginning at the age of 2 or 3 presenting with disturbances of motility and running a subacute course might be difficult to distinguish from the form of diffuse sclerosis which is the subject of this paper.

Pathological.—The *histological characteristics* of this disease may be

summarized briefly: (1) There is a disappearance of myelin and probably also faulty myelination, affecting first and most those areas of the brain and those projection systems which are normally unmyelinated at birth and especially those in which myelination is delayed until after the third month of extra-uterine life. This selectivity is exemplified by the comparative sparing of the optic radiations, olfactory tracts, fornix, vermis and antero-superior part of the cerebellar hemispheres and by the less complete demyelination of the pyramidal tracts and the projection fibres to the post-central cortex than of the fronto-pontine and temporo-pontine systems.

(2) This demyelination is associated with a very early and apparently primary disappearance of the interfascicular oligodendroglia which in some cases had disappeared from tracts and fibre systems which showed no evident demyelination. This was most clearly seen in the brain-stem in Case 3 and in the brain-stem and cord in Case 4.

(3) The breakdown of myelin assumes a very abnormal form. Sudanophil lipid is only seen in the walls of medium-sized vessels and instead of the usual fat granule cells in the white matter there are large numbers of "granular bodies" in some of which the granules stain like myelin with Scharlach, Azan and hæmatoxylin lakes, while in others they are mucinoid in character, staining red with mucicarmine, metachromatically with toluidin blue, blue with Azan and red with the Schiff-Hotchkiss method. The myelin-like granular bodies failed to stain with Baker's modification of the Smith-Dietrich stain for phospholipids, although fine granules scattered through the tissues stained by this method as well as by the Weigert-Pal and Loyez' stain for myelin. It appears likely, therefore, that the granular material represented three breakdown products of myelin: (i) Phospholipid in fine loose granules; (ii) a compound closely related to myelin containing galacto-lipids which was collected at an early stage in the granular bodies; and (iii) a breakdown product of this consisting chiefly, if not entirely, of galacto-lipids which passed through the tissues into the perivascular sheaths of the vessels and was there either absorbed into the blood stream or broken up into simple lipids and fat. (The term "granular bodies" has been used throughout to describe the rounded collections of granules, although it is recognized that some of them have a nucleus and are probably lipid-containing cells. In every case, however, the number of bodies in which no nucleus was visible outnumbered those in which one was seen. While the diameter of the granular bodies was rather greater than the thickness of the sections the disparity was too small to account for this absence of nucleation.)

(4) Abnormal metachromatic material was also found in the nerve cells of the nucleus dentatus and globus pallidus (in frozen sections), in

the portal spaces of the liver and in the looped tubules of Henle in the kidney. This material appeared to be different from sudanophil lipid although this point was not definitely established in the case of the neurons of the nucleus dentatus. It was soluble in absolute alcohol. The metachromatic granular material in these four situations: (i) *white matter* of the cerebral and cerebellar hemispheres; (ii) *neurons* of the nucleus dentatus; (iii) *liver;* and (iv) *kidneys,* differed both in its reaction to other staining methods and, to some extent, in its solubility.

(i) That in the white matter was present in celloidin sections and was faintly anisotropic in frozen sections. It stained with the Schiff-Hotchkiss technique, retaining this stain when the sections were cleared in xylol and mounted in xylol-balsam.

(ii) That in the neurons of the nucleus dentatus was stainable metachromatically in frozen sections, but neither in celloidin sections nor in frozen sections left overnight in absolute alcohol. Granules in the same situation, but apparently in larger number, stained with Sudan IV and with the Schiff-Hotchkiss technique in frozen sections. Lipochrome stainable with the latter two methods was present in control cases but did not stain metachromatically. All these intra-neuronal granules were isotropic.

(iii) That in the liver was isotropic. It disappeared from sections left overnight in absolute alcohol (before staining) although granules in similar situations and also in Kupffer cells, which stained with the Schiff-Hotchkiss technique, remained stainable after this treatment.

(iv) That in the kidney was not stained by any method other than toluidin blue. It was associated with granules which were more brightly anisotropic than any in the central nervous system, but these may have been different from the metachromatic granules. Neither was seen in frozen sections left overnight in absolute alcohol. Control material showed no comparable granules in Henle's tubules.

Discussion of pathogenesis.—The problem of metachromatic leucoencephalopathy has been well discussed by Norman (1947) in his recent description of a familial case. He drew attention to the presence of metachromatic lipid not only as the predominant, histologically visible result of the katabolism of myelin, but also in the neurons of certain brain-stem nuclei, in the gall-bladder and in the kidneys. Einarson and Neel (1942) rightly point out that cases with metachromatic products of katabolism fall into two sub-groups: "(*a*) the *pure metachromatic types,* in which there occurs an enormous accumulation of metachromatic, singly refracting breakdown products, which quantitatively quite dominate the picture —the products lie both in scavenger cells and free in the tissue; and (*b*) the *fatty metachromatic types* showing the picture of mixed occurrence of fat and metachromatic, often doubly refracting products, which in

places may show some mucinoid character." It has become evident that metachromasia occurs, to a limited extent, in all forms of myelin katabolism, if it is looked for under appropriate conditions. If, as is supposed, the metachromasia is given by a galacto-lipid, this is likely to be relatively insoluble in alcohol, but soluble in such solvents as xylol and chloroform. Therefore, whilst most evident in frozen sections, it may also be seen in celloidin sections if the stronger lipid solvents are avoided. In our cases celloidin sections stained by toluidin blue or thionin and cleared in xylol showed no metachromasia, although mucicarmine and Azan stained the majority of the granular bodies well. At a later stage of the examination it was learned that Norman had used frozen sections in his examination and when this technique was adopted in our cases metachromasia was at once evident and could be preserved if the sections were mounted in "microil" directly from alcohol. Re-examination of celloidin material with the same technique showed that the "Azan-blue" granular bodies were metachromatic. Thus, although no metachromasia was found in the two cases of this condition recorded in 1933, we now consider that this was due to the methods employed, since metachromasia of the Azan-blue granular bodies was present in all four cases of the present series. The use of the Schiff-Hotchkiss technique for polysaccharides has confirmed the view that the metachromatic material in the white matter of the brain is a galacto-lipid, but this method is not very specific in that it stains many of the more complex lipids such as myelin, and lipochrome, as well as many of the fat granule cells in areas of ischæmic softening. The Azan-red granules, as well as the Azan-blue, mucinoid granules, stained by this technique.

There need, therefore, be no essential difference in the katabolism of myelin between cases of diffuse sclerosis in which mucocytes or metachromatic lipids are present along with sudanophil lipids, and cases of disseminated sclerosis, vascular softening or Wallerian degeneration. It appears probable that the early publication of cases in which metachromatic or mucinoid lipid predominated drew the attention of neuropathologists to the use of these special staining methods in cases of diffuse sclerosis of the brain, with much consequent confusion.

The name metachromatic leuco-encephalopathy should, therefore, be reserved for Einarson and Neel's sub-group (a), in which metachromatic lipids dominate the picture and where there is little if any sudanophil lipid except in the walls of the vessels. Such cases are much rarer than those showing the more usual form of myelin katabolism. Most have occurred in adults. Carillo's (1933) case, though included by Norman and by Einarson and Neel among the metachromatic cases, does not appear to deserve this classification, as the katabolic products, although not

sudanophilic, stained *green* with thionin. Metachromasia has been found in the lipid in certain nerve cells in many of these cases, a discovery first described by Nissl in 1910. In Norman's case the neurons of the nucleus dentatus, nucleus subthalamicus and oculomotor nuclei were distended with this lipid, so that they resembled those seen in amaurotic family idiocy. No such excess of lipid was present in our cases and metachromatic lipid was only found in the nucleus dentatus, and, in one case, in the globus pallidus. Unfortunately in all cases the part of the mid-brain containing the nucleus subthalamicus and oculomotor nuclei was embedded in celloidin before it was realized that the inter-neuronal lipid failed to stain metachromatically after treatment with alcohol.

W - 1921
N - 1947

Witte's was the only case prior to Norman's in which metachromatic material was found elsewhere than in the brain. He found it in the anterior lobe of the pituitary, in the liver, the testes and the convoluted tubules of the kidney, both within the epithelium and as intratubular casts. In our case the material in the kidney was confined to the looped tubules and differed from the metachromatic material in the brain and liver in failing to stain by the Schiff-Hotchkiss technique, although intratubular casts and granules on the margin of the convoluted tubules stained by this method both in Case 4 and in controls.

The different reactions to different staining methods given by the metachromatic material in different situations (white matter of the brain, neurons of nucleus dentatus, liver and kidneys) are rather confusing, but clearly indicate that it is not all of the same character, although all is soluble in fat solvents and therefore presumably of lipid character. The derivation of the metachromatic material in the white matter of the brain from a myelin-like substance is evident enough from the gradation of the granular bodies from Azan-red to Azan-blue, and this material is therefore almost certainly a galacto-lipid. The metachromatic material in the neurones of the nucleus dentatus might, as was suggested by van Bogaert and Dewulf, be closely related to lipochrome, but the fact that no metachromasia was given for example by the lipochrome in the cells of the inferior olive of Case 4 or by the lipochrome in the nerve cells of the brains of other children of similar age, treated in the same manner (although in every case it reacted positively to the Schiff-Hotchkiss technique), indicates either that some alteration had occurred in the lipochrome in certain neurons, or, more probably, that the metachromatic intra-neuronal granules were separate and different from the lipochrome granules.

The metachromatic material in the kidneys presented a special problem owing to the difference in staining reactions to toluidin blue and to the Schiff-Hotchkiss technique. It is, of course, recognized that while both methods stain mucinoid and polysaccharide material the reaction

is not given by the same part of the molecule in the two cases. Metachromasia is considered to be due to the presence of sulphuric esters, while the Schiff-Hotchkiss staining with basic fuchsin is due to oxidation of the 1.2.glycol grouping to a dialdehyde.

The characters of the metachromasia in the liver, taken along with the results given by the Schiff-Hotchkiss technique, suggest absorption of galacto-lipid from the blood stream and some katabolism of this by the epithelium and Kupffer cells of the liver. Of the katabolic products, one still giving metachromatic staining may be excreted by the looped tubules of Henle in the kidney, while the other is further broken down in the liver. This suggestion does not explain the brilliant anisotropism of the tubules of Henle in these cases, but the facts that it is much more brilliant than the anisotropism related to metachromatic material elsewhere, and that the transmitted light is colourless, suggest that the metachromasia and the anisotropism may be due to two different substances, both of which are soluble in alcohol, though neither stains with Sudan IV.

The application of new staining methods, and, in consequence, the more exhaustive histological examination which it has been possible to make of these four cases has brought to light certain further characteristics which appear to be common to the group. These new facts, however, do not help greatly towards deciding the question whether the disease is one of the nervous system primarily, or, as Witte suggested in discussing his case of metachromatic leuco-encephalopathy, of more general character. As Norman has pointed out "the metachromatic material appeared to be acceptable to the cerebral vessels without prior transformation into neutral fat," in his case, and this was also true in ours. It is therefore possible that the metachromatic material found in the liver and kidneys was formed in the brain. The suggestion made in the report on the two earlier cases (Greenfield, 1933) that the demyelination of the brain might, at least in part, be due to faulty supply of lipids from the blood during the process of myelination, receives some support from the work of Waelsch, Sperry and Stroyanoff (1941) who showed, by the use of heavy water (D_2O), that lipids are deposited in the brain before myelination takes place there, and that the synthesis of myelin, presumably from these lipids, occurs in the brain itself. That the myelin throughout the nervous system may be poorly formed in this type of encephalopathy, and may therefore be less stable than normal, is borne out by the condition of the spinal nerve roots in Case 4, where granules of myelin-like material lay in large collections between the myelinated fibres. The nature of this disturbance of myelin formation is not known, but the histological appearances suggest that it is

associated with a relative excess of galacto-lipid and a poverty in phospholipid and cholesterol.

The arguments favouring the oligodendroglia as the factory for myelin were put forward in the report on the two earlier cases (Greenfield, 1933) and it was considered probable that the oligodendroglia also undertakes the nutrition of myelin. The close relationship of oligodendroglia to myelin metabolism is generally accepted at the present time. It is well known, for example, that it soon disappears from an area of demyelination, whatever the cause of this may be. Degeneration and disappearence of oligodendroglia is therefore common in diffuse cerebral sclerosis. But in no other cases which have come under the observation of the authors has the disappearance of oligodendroglia preceded demyelination. This is the most characteristic abnormality in this form of cerebral sclerosis. It is impossible to decide to what extent the myelin degenerates owing to the failure of the nutritive action of the oligodendroglia, and to what extent the latter either fails to mature or degenerates early owing to some abnormality in the constitution of the myelin. That the disappearance of oligodendroglia is, in part at least, due to degeneration of previously existing cells is indicated by its more complete disappearance in Case 4 in which the disease was allowed to proceed to its natural end, than in Cases 1 and 2 which terminated at an earlier stage owing to surgical intervention.

Any theory of the pathogenesis of the disease must take account of the topographical relationship of the demyelination to the myelination of the human brain after birth; but this favours equally the cellular and the humoral theories, since maturation of the oligodendroglia proceeds *pari passu* with myelination. The relationship of the disease to metachromatic leuco-encephalopathy in older subjects, whether familial or not, must also be taken into account; but, although resembling these cases in some respects, the disease, in the 6 cases described, is remarkably stereotyped both in its clinical and pathological aspects, and deserves a separate nosological position from all the other conditions which have been grouped together under the term "Diffuse cerebral sclerosis."

Summary

(1) Four new cases are described of the condition described in 1933 under the name "A form of progressive cerebral sclerosis in infants associated with primary degeneration of the interfascicular glia."

(2) The disease in all the children commenced during the second or early in the third year of life and was fatal between the ages of 2 years and 9 months and 3 years and 1 month. The early symptoms were disorders of motility and equilibrium: the special senses were rarely affected, and dementia was a late symptom.

(3) Naked-eye examination of the brain showed no abnormality except diffuse firmness of the white matter of the cerebral and cerebellar hemispheres. Demyelination was not evident on section.

(4) Histologically the disease is characterized by

(*a*) Complete disappearance of the interfascicular oligodendroglia from the white matter of the cerebrum, and partial or complete loss of these cells from many areas in the brain-stem, cerebellum and spinal cord, which show no evident demyelinization.

(*b*) The demyelination affects chiefly those fibre systems which myelinate after birth and especially those which are not fully myelinated at 3 months of age.

(*c*) Throughout the demyelinated areas there are numerous rounded collections of abnormal lipid, chiefly galacto-lipid in character. Phosphatides are found only in small isolated granules and in the remaining myelin sheaths. No sudanophil lipid is seen except in the walls of medium-sized and small vessels.

(*d*) The use of toluidin blue on frozen sections shows metachromasia, not only of the "granular bodies" of galacto-lipid in the white matter, but also in the nerve cells of the nucleus dentatus, in phagocytes in the portal tracts of the liver, and in the epithelium of Henle's tubules in the kidney. Brightly anisotropic granules are also seen in the latter situation.

(5) The disease is considered to be a developmental disorder of the lipid metabolism of the central nervous system. The relationship of the apparently primary degeneration of the oligodendroglia to this is discussed.

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LEGENDS FOR PLATES

PLATE XI

FIG. 1.—Coronal section of the occipital lobe of a normal 3-months-old infant, showing the optic radiations as the only myelinated fibres. Loyez stain. × about 1·5.

FIG. 2 (*Case* 2).—Coronal section of occipital lobe for comparison with normal 3-months infant. Weigert-Pal stain. Original size.

FIG. 3 (*Case* 1).—Corpus callosum, to show sparse myelin sheaths and abundant loose granules. Weigert-Pal stain.

FIG. 4 (*Case* 1).—Optic radiations cut in longitudinal section with demyelinated white matter on either side of them. Weigert-Pal stain.

PLATE XII

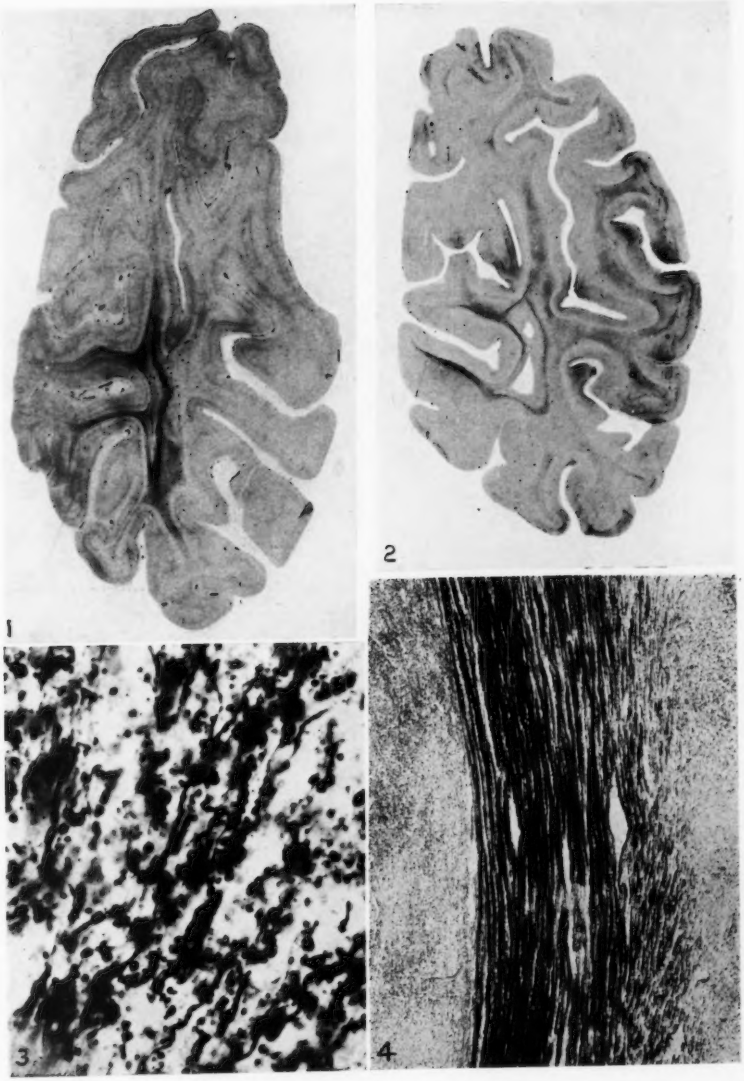
FIG. 5 (*Case* 1).—Corpus callosum showing granular bodies in tissues and collected round a small vessel. Iron hæmatoxylin. Van Gieson. × 350.

FIG. 6 (*Case* 4).—Centrum semiovale stained by the Schiff-Hotchkiss technique, showing numerous granular bodies, free and collected in the perivascular sheath. × 100.

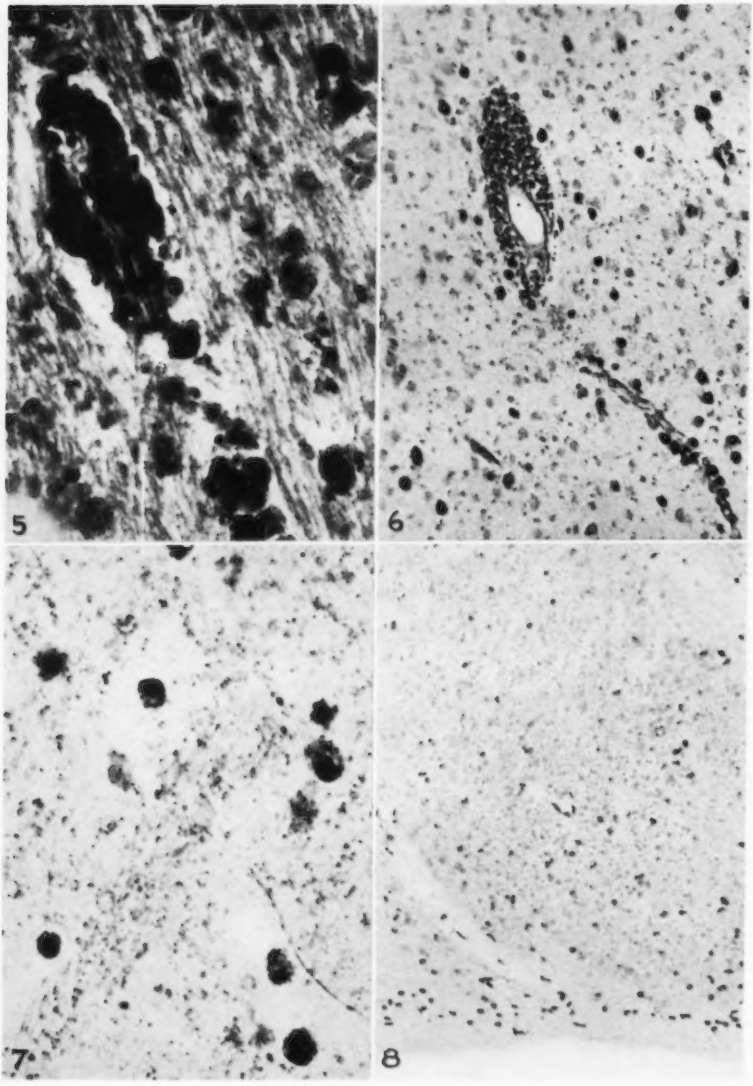
FIG. 7 (*Case* 3).—Subcortical zone of white matter stained by Loyez' method, showing early granular bodies, loose granules of myelin débris and sparse myelinated fibres. × 300.

FIG. 8 (*Case* 4).—Dorsal columns of the cord showing absence of oligodendroglial nuclei. Iron hæmatoxylin. Van Gieson. × 100.

PLATE XI



To illustrate article by W. Russell Brain and J. G. Greenfield



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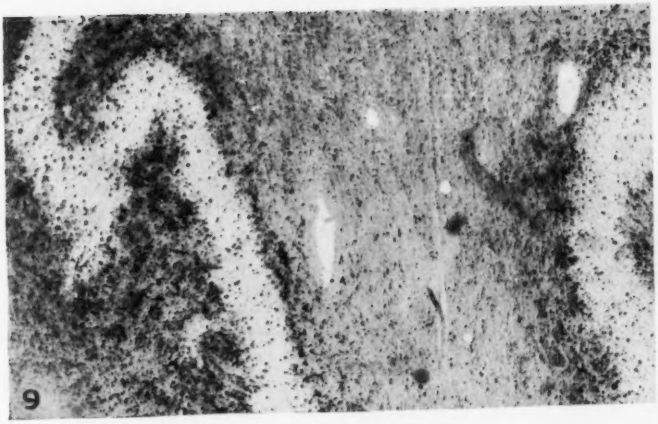

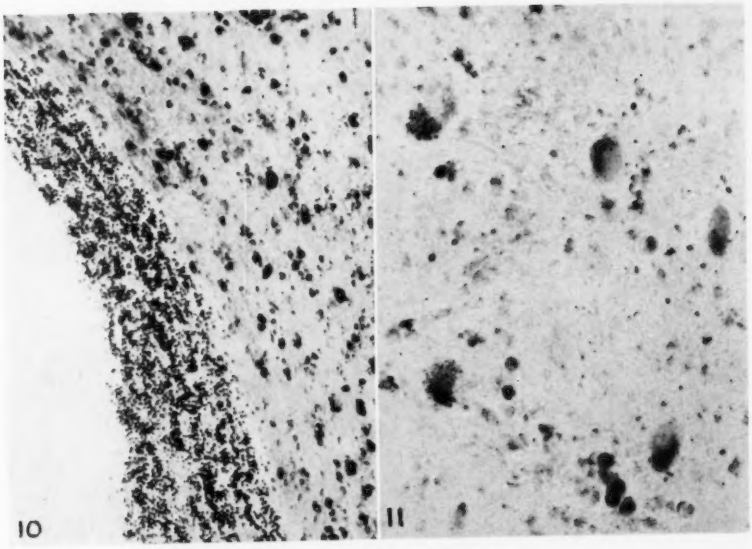

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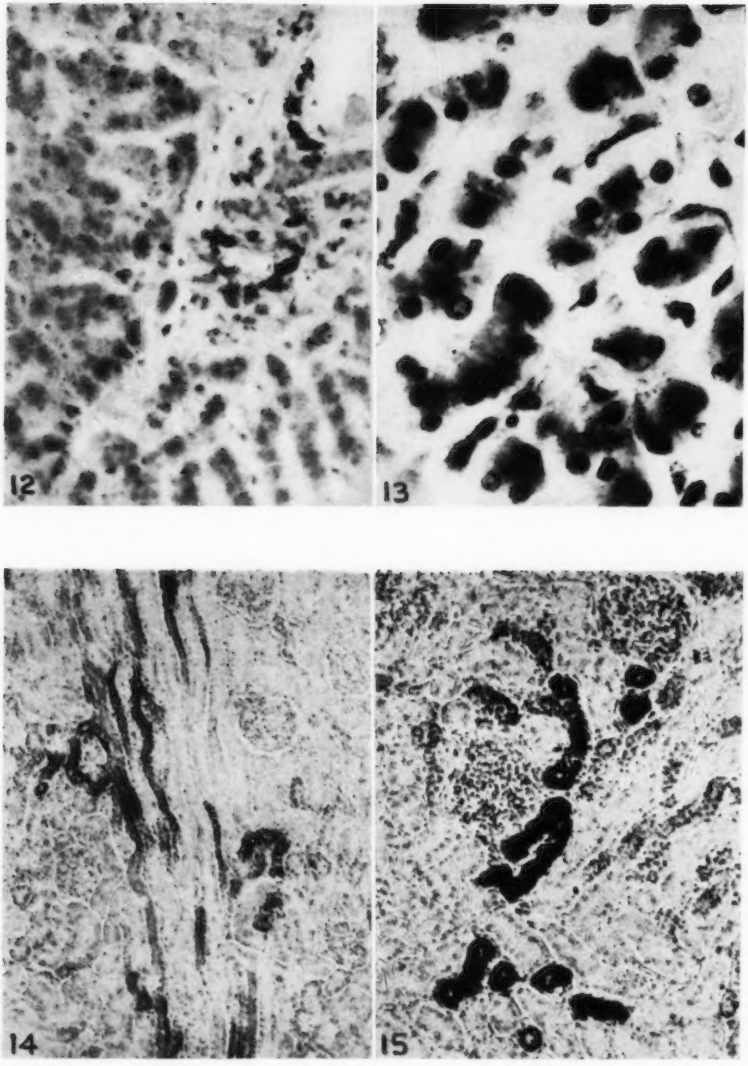

To illustrate article by W. Russell Brain and J. G. Greenfield

PLATE XIII

Frozen sections of cerebellum of Case 2, stained with toluidin blue for metachromasia.

FIG. 9.—Low-power view of the nucleus dentatus showing metachromatic bodies round the nucleus and metachromatic material in its neurones, but very little metachromasia in the hilum. × 35.

FIG. 10.—Cerebellar cortex. The granular layer is normal and the white matter internal to it is filled with metachromatic granular bodies. × 100.

FIG. 11.—Nucleus dentatus. Several neurones are seen containing metachromatic material. × 300.

PLATE XIV

FIG. 12 (*Case* 4).—Liver. Frozen section stained with toluidin blue, showing metachromasia in phagocytes in the portal tracts.

FIG. 13 (*Case* 4).—Liver. Frozen section stained by the Schiff-Hotchkiss technique, showing darkly stained granules in swollen Kupffer cells.

FIG. 14 (*Case* 4).—Kidney. Frozen section stained with toluidin blue showing metachromatic granules filling the epithelium of Henle's tubules.

FIG. 15.—The same section under higher magnification in an area where Henle's tubules are cut more transversely.

MYOTONIA CONGENITA, DYSTROPHIA MYOTONICA AND PARAMYOTONIA; REAFFIRMATION OF THEIR IDENTITY

BY

OTTO MAAS and A. SPENCER PATERSON

It is now ten years since we wrote (1939) giving reasons for our view that myotonia congenita (Thomsen's disease), dystrophia myotonia and paramyotonia were essentially one and the same disease.

Erb (1886) regarded myotonia congenita as an affection of the voluntary muscle system, which usually begins in early infancy and is probably congenital in origin. Its signs are stiffness and hypertrophy of the voluntary muscles, the subjects being in every other respect normal.

Dystrophia myotonica on the other hand, as described by Batten and Gibb (1909), Steinert (1909) and Curschmann, starts not in infancy but between the ages of 20 and 30. Wasting is said to be localized in the facial muscles, sternomastoids, supinators and in the hands, whereas the shoulder-girdle and pelvic-girdle are unaffected. Later there is said to be a disturbance of phonation, and also endocrine and mental changes.

It is worth noting that Kinnier Wilson's view was rather different. He stated (1940) that wasting of muscles could occur in myotonia congenita and that dystrophia myotonica should be diagnosed only when cataract and other signs of degeneration were found. We have already discussed his view (1943).

Examination by one of us (O. M.) of about 700 members of more than a hundred different families affected by myotonia, and by the other (A. S. P.) of over 170 cases, has convinced us that a very large proportion of those affected do not correspond at all closely either to the accepted clinical picture of myotonia congenita or to that of dystrophia myotonica. We have examined cases diagnosed by other neurologists as myotonia congenita, but in each case we have found some features which have necessitated the diagnosis of dystrophia myotonica.

In our previous paper of 1939 we listed those authors who believed that the diseases were essentially the same, and also those who treated them as separate. In the last ten years the view that the diseases are identical have been held by Grinker (1943), Passouant and Minz (1944), Klingler (1948) and by Rouquès, Pautrat and Sainrapt (1947), who wrote "Myotonia without atrophy is nothing but a developmental stage."

On the other hand Julia Bell (1947), Franceschetti (1948) and Thomasen

(1948) have concluded that there is a fundamental difference between the diseases. Some geneticists have accepted this opinion (Ruggles Gates, 1946; Penrose, 1948; Fraser Roberts, 1948; and also Hassin and Kesert, 1948).

J. Bell (1947) collected and analysed all the available material in the literature. She writes (p. 364):

"Though it is true that early cases of dystrophia myotonica may show no sign of disease apart from myotonia, there are so many fundamental differences between typical cases of the two conditions that we find it impossible to conceive them as the same disease arising from the same source. In a fully developed case of Thomsen's disease, myotonia is the predominant and only disabling symptom; in dystrophia myotonica muscular weakness and wasting become the predominant features, and myotonia, though it may be troublesome and inconvenient, is relatively of subsidiary import to the patient. I would ask the reader who has doubt regarding the differentiation of the two diseases to read Birt's[1] account of Thomsen's disease in himself and consider whether he could recognize there any affinity to the history of cases of dystrophia myotonica. The point is not whether a particular individual with the one disease can be found at one stage of his affection to resemble an individual with the other disease, but whether a typical series of the one affection shows the same characteristics as a typical series of the other affection with regard to such essential determinants as age of onset, course and prognosis, signs and symptoms accompanying defects and genetic source."

Bell gives in Table XVIII the "main features of Thomsen's disease and of dystrophia myotonica" as she conceives them.

	Thomsen's disease	*Dystrophia myotonica*
(1) Age of onset	Usually congenital	75 per cent after 15 years
(2) Myotonia	Widespread	Usually over restricted areas
(3) Muscular signs	Hypertrophy common	Marked weakness and wasting in characteristic areas
(4) Cataract	No association	Frequent association
(5) Baldness	Not a characteristic	Characteristic
(6) Testicular atrophy	Not a characteristic	To be expected
(7) Tendon reflexes	Usually normal	Usually lost early in disease
(8) Mental condition	Associated psychosis	Deterioration common
(9) Genetic basis	Dominant, suppression rare	Dominant, suppression often demonstrable

In what follows we shall examine each of these points in detail. We think that by so doing it will become evident that Bell's differentiation of myotonia congenita and dystrophia myotonica is not valid.

(1) *Age of onset.*—Although Bell states that onset in infancy is a feature of myotonia congenita, many writers describe a later onset. Thus Case 3 of Erb (1886) showed his first symptoms at 16 and one of Ballet and Marie's (1883) at 10. Erb stated that this last was a typical case. Thomasen also (1948) (p. 53) mentioned cases which began at 12 and even at 20.

On the other hand it is not at all unusual for the children of known cases of dystrophia myotonica to develop myotonic signs in infancy or

[1]For fuller discussion *see* footnote, page 327.

early childhood. Steinert (1909) and Huebner (1917) both described symptoms of dystrophia myotonica as occurring in infancy in members of families suffering from the disease. Herner (1940) as well as Gorina and Cruz (1948) have also described the onset of dystrophia myotonica in childhood. Franceschetti, Klein and Walthard (1948) while stating that dystrophia myotonica began between the ages of 20 and 50, yet themselves (p. 161) observed myotonia in such a case as early as 6 years of age.

Although Curschmann stated that severe and complete cases of dystrophia myotonica never started in early infancy, yet he and Grund (1910) described cases which started before the age of 10.

In our own series a number of cases of dystrophia myotonica had children who showed symptoms of myotonia and sometimes of wasting in infancy.

Thus in Family 112 a woman who together with a brother and sister was affected by dystrophia myotonica had a son of 5 who already showed myotonia in the tongue, facial weakness, stiffness of the legs and baldness. In Family 94 a man had dystrophia myotonica with cataract. Of his 3 sons, one aged 8 had myotonia in tongue and hands, one aged 6 had slight myotonia, and one aged 5 had definite myotonia in the tongue and slight myotonia in the thenars. In Family 114 a woman with typical dystrophia myotonica had a daughter of 10 showing stiffness in the hands since infancy. She had typical myotonia in the tongue and right thenars and both hypothenars and slight wasting in the lateral parts of both thenar eminences. In Family Re. No. 1 in which many cases of dystrophia myotonica occurred, a girl aged 13 showed definite myotonia of the tongue and thenars, and also slight weakness of the facial muscles. A. M. (Family 121) was a case of dystrophia myotonica and his daughter of 2 had typical myotonia in the hands. Family Th. (No. 115) is also noteworthy. As a brother of Mrs. Th. suffered from myotonia and definite wasting of muscles, the diagnosis for this family is dystrophia myotonica. Mrs. Th. and her sons of 8 and 4 all suffered from myotonia in early infancy. Neither in Mrs. Th. nor in her sons, however, was definite wasting of muscles observed.

Conclusion.—Examination of numerous pedigrees, then, shows that children belonging to families affected by dystrophia myotonica frequently show symptoms in infancy, while many cases described in the literature as Thomsen's disease have shown their first symptoms at a later stage.

(2) *Myotonia.*—Bell writes that in Thomsen's disease, myotonia is widespread, but in dystrophia myotonica it is usually only "over restricted areas." Thomasen states that as a rule in Thomsen's disease all striated muscles are affected, and Franceschetti also agrees.

Reference to the literature, however, does not bear out Bell's thesis. Gaupp (1900), Heymann (1918), Stiefler (1922), Rimbaud et Jourdan (1922) and Oppenheim (1923), all describe cases diagnosed as Thomsen's disease in which the myotonia was restricted to certain areas. Osler (1909) referred to 3 cases described by Hammond in which Thomsen's disease began at the age of 8 and was confined to the arms.

On the other hand it is not uncommon to find cases of dystrophia

myotonica in which the myotonia is widespread. In Bell's own monograph, we read Purdon Martin's account of myotonia in dystrophia myotonica as follows: "It occurs most characteristically in the small muscles of the hands, the tongue and facial musculature, but it may affect any part of the body and in severe cases occasionally causes the patient to fall like a log, muscle-bound."

A. M. (Fam. 121), a man of 28 who had a myopathic facies and winging of the scapulæ, stated that at times he remained for four or five minutes rigid like a statue and unable to move any limb, as all were locked and muscle-bound.

Denny-Brown and Nevin (1941) described a case thus: "Generalized myotonia was associated with universal hypertrophy of musculature, especially that of the forearms and hands. He had early opacities in the lenses in both eyes." We would regard this as a case of dystrophia myotonica. Several such cases have been described in the literature (Adie and Greenfield, 1923).

Horányi and Pohl (1942) as well as Franceschetti, Klein and Walthard (1948) (p. 186) also observed widespread myotonia in dystrophia myotonica.

Conclusion.—Contrary to Bell's views, myotonia in cases of Thomsen's disease is often limited to a few muscles. On the other hand, like many others, we have seen widespread myotonia in the early stages of many cases of dystrophia myotonica. When the wasting of muscle progresses, however, myotonia tends to disappear.

(3) *Muscular signs.*—According to Bell, hypertrophy is common in Thomsen's disease, but marked weakness and wasting in "characteristic areas" is typical of dystrophia myotonica. Gammon, Harvey and Masland (1941) also stated that all voluntary muscles were hypertrophied in Thomsen's disease.

Again, however, reference to the literature shows that many cases diagnosed as Thomsen's disease have not shown any hypertrophy of muscles (Wichmann, 1897; Mingazzini and Perusini, 1904; te Kamp, 1907; Knoblauch, 1909).

On the other hand, we have seen many cases of muscular hypertrophy in indubitable cases of dystrophia myotonica. One man had won prizes for running in the Army, but, when seen, had some atrophied muscles. Case A. M. (Family 121) showed marked hypertrophy of some muscles and yet had winging of the scapulæ. Thomasen also (p. 189) observed a few cases of dystrophia myotonica in which there was "localized hypertrophy."

Breitford (1938) described a case in which there was a generalized well-developed musculature except for the lower limbs and also the hands

which were atrophic and weak. He diagnosed the case as one of Thomsen's disease. This is surprising, for the association of hypertrophy with weakness and wasting is common in dystrophia myotonica.

With regard to the localization of muscle-wasting, it is true (cf. Steinert, Curschmann and others) that the sternomastoids, supinators, facial and hand muscles are often affected. In numerous cases, however, these muscles remain unaffected. We supported (1939) Adie and Greenfield's (1923) view that wasting and weakness do not always arise in "characteristic areas." Very different muscles are wasted in different cases. We have seen, for example, early wasting in the shoulder and in the pelvic girdle in some cases, in which the facial muscles escaped. Various writers, e.g. d'Antona (1926), Krause and Ellenbeck (1930), Rohrer (1916), have reported cases of dystrophia myotonica in which the wasted muscles were different from those regarded by Steinert (1909) and others as typical.

There is no doubt that when one examines not merely a few severe cases of dystrophia myotonica but a large number of their relatives, whether slightly or severely affected, one finds that the symptoms are very much more polymorphic than are generally supposed.

We have found varying degrees of hypertrophy of muscles in the early stages of dystrophia myotonica which diminish with the progress of the wasting.

It is of interest that Gallot Scherrer and Bourguignon (1948) described a family affected by "a variety of hereditary dystrophy of muscles" in which the grandfather had a combination of hypertrophy and wasting, while the father and patient had hypertrophy alone.

(4) *Cataract.*—Cataract, according to Bell, occurs only in dystrophia myotonica.

She does not go as far as some other writers in saying that cataract occurs in every case of dystrophia myotonica, e.g. Franceschetti, Klein and Walthard (1948), who say that it never occurs in Thomsen's disease. Vogt (1931) said that a slit-lamp revealed cataract in each case. Allen and Barer (1940) found it in all of 21 cases examined by slit-lamp, and Sautter (1941) in 28 cases, but he found no cataract in 4 more cases diagnosed as Thomsen's disease. Girardet and Ott (1947, 1948) and Faber (1949) wrote in a similar sense.

We published (1939, 1947) several cases of dystrophia myotonica in which experts did not find a cataract. We expressly mentioned (1943) that the examinations were carried out by slit-lamp; although Franceschetti *et al.* (1947) say that we did not mention this. In addition we may mention case A. M. (Fam. 121) who had generalized myotonia and winging of the scapulæ but no cataract (s.l.e.) and also Mrs. L. M., aged 31, Fam. 97. Her father had typical dystrophia myotonica with cataract, whereas she

felt healthy, but had myotonia in her tongue and both thenars together with wasting of the right thenar muscle. She had no cataract (s.l.e).

Other writers, too, have described cases of dystrophia myotonica in which no cataract was found even on slit-lamp examination. Thus Dereux and Baudu (1938) described a case with typical signs of the disease, but no cataract (s.l.e.) although cataract had been found in one parent and grandparent. Paulian and Tudor (1940) also reported a case which they called "myotonia atrophica frustra," in which there was no cataract. Baruch (1933) examined two brothers to whom he gave the diagnosis "dystrophia myotonica sine dystrophia." Only in the younger one a trace of cataract ("minimale Linsentrübung") was observed. As the examination was carried out by a reliable eye-surgeon, the absence of cataract in the elder one of these brothers is beyond doubt. L. van Bogaert (1933) described a case which he called "myotonic myopathy" which was free from cataract on slit-lamp examination. Ravin and Waring (1939) examined a man affected by cataract, but not by myotonia, whereas his father was affected by myotonia but free from cataract (s.l.e.). Thomasen (1948) examined 6 patients affected by wasting but free from cataract. Gorina and Gisbert Cruz examined 4 cases of dystrophia myotonica free from cataract (1948) (cf. also Levy (1948) whose patients were examined by slit-lamp (personal communication)).

Absence of cataract in cases of dystrophia myotonica was also reported by Curschmann (1922).

In some families affected by dystrophia myotonica cases were found with cataract but their muscles were not atrophied but hypertrophied. Sautter (1941) reported such a case, and Klingler (1948) mentioned a case observed by Rohrer (1916).

Opinions differ as to whether the type of cataract seen in cases of dystrophia myotonica is typical or whether the same type of cataract may be observed in other diseases. Vogt (1931) believed in the specificity of this form of cataract, whereas Duverger et Velter (1939) quoted several authors who maintained the contrary. Tschopp (1933) also wrote that the question was still in doubt, while Franceschetti (1942) stated that there were definite differences between myotonic and tetanic cataract.

C. Goulden (1928) pointed out the similarity of cataract in cases of dystrophia myotonica, traumatic myxœdema, post-operative tetany, mongolism and cretinism.

Opinions also differ as to whether the type of cataract is the same in all cases of dystrophia myotonica.

Bell (p. 360) wrote: "There is no evidence of any liability to cataract in members of families with Thomsen's disease or with paramyotonia." It is doubtful whether this statement means very much, as dystrophia myotonica is always diagnosed when cataract is found in conjunction with myotonia or paramyotonia, even where atrophy of muscles is not obvious.

Conclusions on the association of cataract with dystrophia myotonica.— The absence of cataract in cases of dystrophia myotonica is not very

exceptional. We do not agree with Franceschetti, Klein and Walthard who say that they are constantly associated. Certainly it is impossible to say that in a particular case a cataract will not come on at a later date. We did notice that in most cases (though not all) (cf. Case A. M. Fam. 121) the wasting was relatively mild.

(5) *Frontal baldness.*—Frontal baldness, according to Bell, is not a characteristic of Thomsen's disease, whereas it is a characteristic of dystrophia myotonica. Frontal baldness is certainly a frequent accompaniment in the later stages, especially in males. It begins usually in the lateral part of the frontal region. We noticed, however, an absence of baldness even in the later stages in some males, e.g. Alex W. aged 27 (Fam. 119) who had had stiffness since the age of 6. He now had myotonia in arms and legs; sternomastoids and temporals wasted; myopathic facies; speech indistinct, yet no trace of baldness (cf. Krause and Ellenbeck, 1930).

(6) *Testicular atrophy.*—Testicular atrophy, according to Bell, is not characteristic of Thomsen's disease, but is to be expected in dystrophia myotonica.

The real truth is, however, that dystrophia myotonica is always diagnosed if testicular atrophy occurs, e.g. Steinert (1910) altered his diagnosis in one case who had had myotonia for some years when the symptom appeared. Furthermore the symptom is not always present in dystrophia myotonica, particularly in the early stages (cf. Maas (1937) who mentions (p. 503) cases in which paternity occurred at an advanced stage of the disease). For these reasons we cannot agree with Bing (1948) who insists that testicular atrophy occurs in every case.

(7) *Tendon reflexes.*—Bell stated that tendon reflexes were usually normal in Thomsen's disease but were lost early in dystrophia myotonica.

This view, however, is not wholly in accord with even the earliest reports on so-called Thomsen's disease, for Erb's three cases in his famous monograph were considered both by himself and by later writers as typical cases of Thomsen's disease. Yet in the first case the knee-jerks showed quick fatigability and were even abolished for a time, while in the second case the knee-jerks were weak and they varied from day to day.

Many other cases reported as Thomsen's disease showed abnormal and absent tendon reflexes (Pontoppidan, 1884, "Very weak reflexes"; and Loeb, 1917, "completely absent knee-jerks"); Singer (1917) "right ankle-jerk abolished, left diminished, sternomastoids extremely atrophic, deltoids hypertrophic."

The following case is typical of how the early stage of dystrophia myotonica may be diagnosed as Thomsen's disease. Curtius (1935) described the niece of a case of dystrophia myotonica. For many years she suffered from myotonia alone and was diagnosed as Thomsen's disease.

but later her ankle-jerks disappeared and he wrote "es haben sich also Veränderungen im Sinne einer myopathischen Komponente entwickelt." This case then appears to be one in which a transition occurs from "myotonia congenita" to "dystrophia myotonica" which Curschmann stated was never found (1939).

We have already (1947) emphasized that tendon reflexes remain active for a long period in many cases of dystrophia myotonica.

Conclusion.—In view then of the evidence listed above, we believe that it is not possible on the basis of the presence or absence of deep reflexes to separate "dystrophia myotonica" from "myotonia congenita."

(8) *Mental condition.*—According to Bell, "associated psychosis is common in Thomsen's disease, whereas mental deterioration is common in dystrophia myotonica."

This statement receives no support from other writers. Psychosis or mental deterioration may be present or absent in each syndrome. All are agreed that mental symptoms may occur in dystrophia myotonica. Franceschetti (1942) said they nearly always occurred; Stolba (1947, 1948) said that they were frequent; we ourselves (1937) have described a number of different mental syndromes in the disease, while we have also mentioned that some cases are normal and even highly intelligent (cf. also Parker, 1948, who describes a psychopathic case).

With regard to Thomsen's disease, Stolba (1947, 1948) stated that psychic changes were not found, while Liebenam (1939) described them as present. Numerous persons in Dr. Thomsen's own family were affected mentally (Thomsen, 1876). Nissen (1923) and Sanders (1935) describe mental deterioration in another family.

Here again, therefore, Bell is alleging a difference which appears to have no foundation in fact.

(9) *Genetic considerations.*—On p. 344, op. cit., Bell writes regarding the relation of myotonia congenita to dystrophia myotonica: "A glance at the pedigrees appended will suggest that from the genetic standpoint there is some basic difference between the groups corresponding respectively to Thomsen's disease and dystrophia myotonica."

In her monograph Bell describes many pedigrees which were published before 1909 when Batten and Gibb and also Steinert first described dystrophia myotonica. The question arises as to how far these early case histories can usefully be quoted in support of the thesis that there are two diseases. Erb (1886) wrote "Typical cases of Thomsen's disease are characterized by myotonia and very marked hypertrophic development of the voluntary muscles in contrast to relatively poor strength, whereas the other functions of the body are normal and the patients are in particular free from any other disturbance of the nervous system."

Now all the pedigrees described by Bell as of myotonia congenita, with the exception of those of Rosett (1922) and of Stattmüller (1923) date from the period between 1886 and 1909. These earlier authors describe patients either as having myotonia alone or else occasionally as having some absent knee-jerks or some form of weakness or atrophy. Bell, however, classifies all these as myotonia congenita.

It is certainly wrong to classify cases with absent deep reflexes, wasting and some atrophy as myotonia congenita, and these are the cases which we have quoted to support our thesis. It would also seem to be fallacious to quote in support of the thesis that myotonia congenita is a separate disease, cases in which the patient has brothers or sisters with dystrophic symptoms. Yet Bell quotes a number of pedigrees in which there are cases with myotonia alone but with near relatives showing dystrophic symptoms. One member of the Thomsen family examined by Schultze and later by Steinert, definitely suffered from dystrophia myotonica (Schiefferdecker and Schultze, 1903, and Steinert, 1909).

In the pedigrees of Boeters also, which are classified by Bell as myotonia congenita, other members of the pedigrees show dystrophic symptoms.

Thus in Bell's fig. 1,021, Case III, 17, a brother, is described as a typical case of Thomsen's disease, while a sister has dystrophic symptoms but no myotonia. In fig. 1,030, Case III, 14, is described as one of typical Thomsen's disease, but his older brother has endocrine and dystrophic symptoms. In fig. 1,035, Case IV, 26, is described as a typical case of Thomsen's disease. Two relatives in previous generations, however, had become affected by cataract, one becoming blind in middle age and the other at the early age of 16.

In fig. 1,027, Case II, 9, showed marked dystrophic symptoms, while two older sisters were said to have myotonia alone. In fig. 1,029, Case III, 2 (wrongly marked II, 2), is described by the recorder as a case of myotonia with marked dystrophic symptoms. Yet two siblings, namely Case III, 1 (wrongly marked II, 1) and 4, were not known to have shown signs of disease other than myotonia although the latter, a male, died at the age of 45.

In fig. 1,031, Case III, 6, is said to have myotonia associated with marked dystrophic signs, but an older sister and another relative had cataract. He had a cousin who at the age of 49 was said to have myotonic symptoms without noticeable dystrophy. A paternal uncle at the age of 40 was mildly affected, as well as a paternal aunt who had died.

Thomasen (1948) also describes members of the Thomsen family, but some of these show signs suggestive of dystrophia myotonica. Although he says (p. 65) that there were no cases of cataract, two pages later he mentions one member who had a very slight star-shaped opacity in the posterior cortex of the lens, while one or two fine white grains were seen in the centre of the lens. On page 71 op. cit. again, we find that in a man of 39, a member of this family, there were some "grey-white grains spread in the lenses without characteristic localization or appearance."

With regard to our own material, the following cases demonstrate further the close relationship between dystrophia myotonica and the Thomsen's disease syndrome in the same families.

Family Asp. (No. 94) (Bell, fig. 845, p. 372 and Plate 45.)

Cecil A. Asp., a male aged 48, a patient of Major H. G. Gharland (Military Hospital, Millbank).

He felt perfectly healthy and did not complain of stiffness or weakness, nor of any eye trouble.

He was found to have typical signs of dystrophia myotonica together with a typical, though mild, cataract. This man had three sons: David, aged 8, had myotonia in the tongue and hands; Peter, aged 6, had slight myotonia; and Antony, aged 5, had definite myotonia in the tongue and slight myotonia in the thenars.

Another case was *Mrs. Rosalind B.* (Family 114).

Mrs. Rosalind B. had typical dystrophia myotonica when examined on 6.1.47. Her daughter, Maureen, aged 10 years, had suffered from stiffness in her hands since infancy. There was typical myotonia in her tongue; mechanical myotonia in her right thenars, hypothenars and other hand muscles. Reflexes normal. Nowhere definite wasting of muscles.

Comment.—These cases indicate that the children of parents with dystrophia myotonica develop myotonic symptoms from an early age, if looked for, and that myotonia may appear before any wasting.

Another case was that of *Alfred G. Sm.* (Fam. 82).

Alfred G. Sm. (Bell, fig. 892, p. 383 and Plate 49) was the fourth of 5 sibs and had advanced dystrophia myotonica with cataract. His father William Sm., aged 68, had been operated on for cataract at the age of 65. On examination, there was typical myotonia in the tongue and hands, slight weakness on blowing out the cheeks; supinator and triceps reflexes were absent.

Comment.—In this case the father would have been reported by the relatives as having cataract only. On examination, however, he was found to have myotonia and only some weakness and diminution of tendon reflexes. He might therefore have passed for a case of the Thomsen's disease syndrome but for the eventual onset of cataract. Since, however, his son developed dystrophia myotonica, there is no doubt that the father also suffered from this disease.

When one considers, then, pedigrees both from the literature and from our own series, there is ample evidence that cases diagnosed as myotonia congenita have near relations who show outspoken signs of dystrophia myotonica. It is difficult, therefore, to believe that there is a different mode of hereditary transmission for the two syndromes.[1]

The Significance of Incomplete Cases

We prefer the term "incomplete" to the word "suspicious" which has been used by various authors such as Greenfield (1911), Henke and Seeger (1928) Curschmann and Boeters (1935) to describe cases in which some but not all of the symptoms of dystrophia myotonica occur, or in which the symptoms were very mild.

[1] Bell emphasizes the case of Dr. Birt as a case of typical myotonia congenita, which could have nothing in common with dystrophia myotonica. Although this patient wrote about his own case *before* 1909 when dystrophia myotonica was first described, he mentioned that one of his sternomastoids was larger than the other, and that his calves were thinner relatively than his arms. These facts suggest that wasting was beginning. He also mentioned very severe sweating and although it is common enough in a mild form, a severe degree of it is a recognized symptom of dystrophia myotonica. Furthermore, a sister died in a state of "marasmus," a word which might well be applied to the later stage of dystrophia myotonica.

We have already discussed this problem (1943, *Brain*, **66,** 66-68). One of the difficulties in studying the genetics of dystrophia myotonica is that one does not find in one pedigree a few clear-cut cases of the disease, and the other members unaffected. There are frequently found cases in which such typical symptoms occur as a myopathic facies, definite loss of reflexes, definite weakness, definite slight wasting, or mechanical myotonia. Most of these were examined in their homes, but examination at hospital would perhaps have shown cataract with the slit-lamp or myotonia with an electrical test.

We consider that if these cases are all listed as normal, as Bell has done, then conclusions drawn with regard to mode of transmission may be fallacious.

Myotonia Congenita as an Early Stage of Dystrophia Myotonica

One reason why some neurologists have believed that myotonia congenita is a separate disease is that cases have not been seen over a sufficiently long period.

The following is a case in point. (Maas, *Brain* (1937), **60**, 498; Guttmann and Stokes, *Lancet* (1939); Maas, *Lancet* (1939); Bell, fig. 852.)

Arthur R. Bu., born 1910, Fam. 19, was diagnosed as myotonia congenita in 1932. Guttmann and Stokes examined him in 1936 and in 1939.

Besides myotonia in numerous muscles and delayed pupillary reaction to light, "there was no clear evidence of dystrophy . . . the left sternomastoid was doubtfully smaller than the right. There was flattening of the lateral part of both thenar eminences, and the calf muscles were prominent. These features have been interpreted by Maas (1937) as evidence of dystrophia myotonica, but the interpretation must remain equivocal."

When examined by us in 1936 at the age of 26, we found the following symptoms in addition to those commonly associated with myotonia congenita: Slight wasting of the temporals; cheeks a little thin and weakness on blowing them out; definite wasting of the left sternomastoid; slight wasting in lateral part of thenars; right supinator jerk absent, left diminished; triceps reflex absent on both sides; both knee-jerks diminished and diminished strength on dorsal flexion of both feet. His arms tended to give way when he had a heavy object in his hands. There was excessive and profuse sweating. A year later vibration sense was diminished in the upper and lower limbs and over the chest. There was also slight frontal baldness and slight myopathic facies.

L. D. Bailey reported "obvious wasting of the left sternomastoid."

E. Wolff on slit-lamp examination (17.4.47) described in the left lens a collection of white granules starting apparently at the anterior limb of the anterior Y suture. "These are not the opacities as usually described in dystrophia myotonica but as they occur in this man and his brother, I cannot help thinking that they are associated with the general condition." C. Goulden, however, considered that the changes in the lens are those that can occur in normal people.

The patient had a brother, T. G. Bu., who had rather similar symptoms. Electrical examination showed slight wasting of the left abductor pollicis and changes in the lens similar to those of his brother.

When examined eleven years later, the signs of wasting were still present but had not made very marked progress in either brother.

Comment.—In our view there cannot be any doubt but that this case, which was first diagnosed as myotonia congenita, was in fact a case of dystrophia myotonica.

For other such cases see our article *Brain* (1943), **66,** 69 and 70.

The close relationship between cases diagnosed first as "myotonia congenita" and dystrophia myotonica is demonstrated also by the following case:

J. G. Goo. (Fam. 56) (Bell, fig. 884, Maas and Paterson (1939), *Brain,* **62,** 210, Case 1. R. N. Ironside, *Brain* (1926), **49,** 241). He suffered from stiffness since infancy. At the age of 22 he had "Herculean torso and limbs." Ironside diagnosed "myotonia congenita." We observed at the age of 34 typical myotonia and slight wasting of sternomastoids and thin cheeks, the left triceps reflex was abolished and dorsal flexion of feet was weak. We diagnosed dystrophia myotonica.

The first sign of beginning atrophy in such cases are often the loss of tendon reflexes, as pointed out by Curtius (1935). In our experience this symptom together with weakness of the facial muscles, of the grip and of dorsal flexion of the feet usually are the earliest signs of commencing atrophy. In some cases, however, as Rouquès (p. 95) indicated, tendon reflexes may be abolished, even before muscle strength is notably diminished.

Cases of transition from the one to the other syndrome are not uncommon. Thus Hitzenberger (1920) reported a case diagnosed first as myotonia congenita at 23 but who was five years later diagnosed as dystrophia myotonica on account of facial weakness and wasting which spread five years later to his upper limbs.

Rouquès, Pautrat and Sainrapt (1947) reported a man who at the age of 18 was diagnosed as myotonia congenita, although there was suspicious wasting in some muscles. Sixteen years later, however, the wasting of muscles was obvious and the authors considered that this confirmed that myotonia was merely a developmental stage in the course of the disease. One member of Dr. Thomsen's family (Julius Jansen) who was at first diagnosed as Thomsen's disease, was later demonstrated by F. Schultze to be a case of dystrophia myotonica, Curschmann agreeing with this diagnosis (1912).

Thomasen (1948) in a monograph also separates the two diseases. He writes "Maas and Paterson's foundation for their theory of identity were, as mentioned, of a purely documentary nature. They had not themselves cases that could be labelled Thomsen's disease, but only cases of dystrophia myotonica."

Many of our cases, however, like Arthur Bu., No. 19, described above, had been diagnosed by others as myotonia congenita.

Thomasen cites numerous cases as myotonia congenita, who in fact had wasting of muscles, absent tendon reflexes and other symptoms of

dystrophia myotonica (Table I, pp. 54–56), e.g. that of Hertz (1914) and of Knaur (1936).

Franceschetti, Klein and Walthard (1947) described three cases of Thomsen's disease which they regarded as typical, but which could easily be cases of dystrophia myotonica in the first stage, since in the first case the triceps reflex was abolished in one arm, there was weakness in both hands, and several members of the family were psychotic. In the family of the second case there was cataract and mental disorder, while in the third case a sister of the patient's father had cataract and the patient herself had hypotonia in the hands and fingers. The last symptom is characteristic of dystrophia myotonica.

In addition to the differences stated by Bell, they mention a difference of habitus. "The hollow-cheeked miserable figure of dystrophia myotonica contrasts with the athletic figure of Thomsen's disease."

While the "miserable figure" may justifiably be applied to the latest stages of dystrophia myotonica, many cases of the disease look normal, while cases diagnosed as Thomsen's disease have been asthenic. One of our cases of dystrophia myotonica was a champion runner and another a professional dancer.

The following case illustrates how symptoms attributed by these authors to myotonia congenita can occur in dystrophia myotonica.

A. M., Fam. 121, was first seen at the West London Hospital on 10.1.49. He was a welder. The first symptom, which appeared two years previously, was a change of personality. From being a placid man with bookish tastes, he became suspicious and had outbursts of violent temper, striking his wife and children. He talked to himself and complained of unpleasant head sensations. A year later he began to notice that he could not release his grip from his lamp. At times his legs locked, and at other times every muscle of his body became locked for several minutes. He could not lift heavy weights. He had winging of the scapulæ and his shoulders became rounded. A curious feature was that for the past year there had been a thickening of the supra-orbital ridges and the patient stated that his hands and feet had become larger, though he still wore the same size of shoe. Excessive sweating. Pyjamas soaked each morning and at a dance his jacket was drenched right through.

Family history.—His paternal grandmother was in hospital with paralysis of muscles and cataract from the age of 68. One brother had a leg that became stiff at times and was described as a "lazy leg." His father was unstable and once attempted suicide by hanging. The patient's daughter aged 2 has stiffness of the hands.

On examination.—Pyknic build. Myopathic facies. Supra-orbital ridges prominent. Jaw and tongue normal. No clubbing. Pulse 60. B.P. 120/60. Discs normal. No cataract (s.l.e.). Doubtful diminution of visual fields. Some doubtful central scotomata.

Muscles.—Myotonia seen after gripping a rod. Cramps of legs witnessed.

Reflexes.—Biceps brachii absent on right. Both triceps brachii and supinators absent. Grips weak. Deltoids, pectorales and thigh muscles hypertrophied. Vibration sense diminished. Left testis was one-third size of right but normal in consistency and sensation. X-ray skull and lungs normal. No polyuria. Urine S.G. 1010.

Comment.—This case then has shown the following characteristics said to be typical of myotonia congenita. He was of pyknic build and not "of a thin, miserable habitus," hypertrophy of many muscles, generalized myotonia at times. For some time he showed myotonia without wasting. He had no cataract. He had mental symptoms without dementia, and his daughter had developed myotonia in the hands by the age of 2 years. Characteristics of dystrophia myotonia, however, are the following: His paternal grandmother was probably affected. There was marked wasting and weakness of some muscles with winging of the scapulæ and very severe hyperhidrosis.

The point which this case illustrates is that there are not two different typical syndromes to which a case of myotonia will belong. The typical syndrome of "myotonia congenita" is so rare as almost never to be found. This type of mixed case is, however, much more typical, and this is what we would expect if "myotonia congenita" is merely the early stage of "dystrophia myotonica."

Other Abortive Forms of Dystrophia Myotonica

One reason why Bell and others have separated myotonia congenita as a special entity is that in some families there is a tendency for myotonia to persist for an unusually long period. It has in fact been pointed out by numerous writers, such as Bing (1909, 1912), Bielschowsky (1921) and Jendrassik (1911) that each family affected by hereditary disease shows peculiarities of its own and this accounts for the fact that myotonia may persist for an unusually long time in some stocks, that is, in some members of particular families. The fact remains, however, that even in these cases themselves some degree of wasting will occur in time, while in other members of the family more typical cases of dystrophia myotonica will occur.

It would indeed be illogical to separate out the Thomsen type of dystrophia myotonica as a special disease and not also those cases in which mild wasting persists for many years and does not go on to marked atrophy and endocrine changes.

The following is a case of dystrophia myotonica in which symptoms of wasting and myotonia occurred at an early age but which did not run a progressive course. We consider that this is analogous to those cases which are generally diagnosed as Thomsen's disease (*see Brain*, **66,** 75).

XY, Fam. 67, a scientist, did not consider himself to be sick but was capable of heavy work, even of a physical character. In 1938 he was 26 years of age and had felt stiffness in his arms for some years. Frontal baldness present since 14. If he moved his head quickly, there was strabismus and diplopia. He soon tired when swimming. He suffered from hyperhidrosis since childhood.

He was an only child. Father aged 61 had had cramps for some years but

capable of hard physical work for many hours in the day. Three sisters of his father probably affected. The youngest, an idiot, died in infancy. One sister of his father had cramps and was slightly bald. All of her children lost their teeth before the age of 21. (For this symptom cf. Rohrer, 1916; Maas and Zondek, 1920; Hirschfeld, 1925; d'Antona, 1926; and Rouquès, 1931.)

On examination.—Myotonia in the tongue; mild myotonia in hands and forearms; slight wasting of temporals; slight facial weakness; slight weakness on dorsal flexion of the left foot; vibration sense diminished; tendon reflexes in the arms diminished.

XY remained in the same condition for at least ten years after the first examination. He had married and had a family of two.

This case appears to be a *forme fruste* of dystrophia myotonica. The interest of the case lies in the fact that so-called Thomsen's disease is not the only abortive form of dystrophia myotonica.

We may mention that as Davenport and Muncy pointed out in 1916, Huntington's chorea manifests itself with rather different symptoms in different families but remains nevertheless one of the same disease.

The Classification of Paramyotonia

This is the name given to the condition in which myotonia results from cold. Julia Bell (op. cit., p. 365) wrote:

"With regard to paramyotonia the material is too scanty for any definite conclusion to be drawn. The effect of cold on myotonia from any source is often very marked, but that the condition should only manifest itself under the influence of cold certainly places the condition in a different category from that characteristic of Thomsen's disease."

Examination of the literature, however, makes this supposition of Bell's very unlikely. The two cases of myotonia congenita, for instance, described by Delprat (1892) occurred in a family, several members of whom suffered from paramyotonia. Pelz (1907) mentioned other families in which some members had paramyotonia and others myotonia. A. H. Hübner (1917) also reported a similar conjunction of cases in one family. Severin (1917) diagnosed two brothers as suffering from myotonia congenita. Cold and rainy weather increased the disturbance in one of them but failed to do so in the other. In a family reported by Knaur (1936) some cases were diagnosed as Thomsen's disease, while several others had paramyotonia.

Schott (1936) published a paper entitled "On Paramyotonia Congenita." He described a family in which both paramyotonia and wasting of muscles were associated. Soelder (1895) described paramyotonia in a family, one of whom had cataract. In both these last two families mentioned, paramyotonia would appear to be associated with dystrophia myotonica (*see also* Maas and Paterson, 1939, Case E. M., p. 207, Family 12, in which

paramyotonia occurred in a family affected by typical dystrophia myotonia).

As early as 1889 Erb argued that the celebrated case of Martius and Hansemann with paramyotonia was merely a variant of Thomsen's disease. Pelz (1907) stated that the frequent occurrence of myotonia congenita and paramyotonia in the same family, and often in the same person, proved their close relationship. Serog (1930) and Boeters (1935) (p. 11) agreed with this.

In this connexion we should like to repeat an observation of Erb (1886). Erb was considering the case reported by Vigouroux (1884) in which "Thomsen's disease" was associated with muscular dystrophy. Erb stated that it was very improbable that two quite different diseases should affect one and the same patient. If they really were different diseases, it would be very difficult to explain their frequent co-existence not only in the same family but in the same individual.

If, as Bell suggests, paramyotonia belongs to a different category, then logically she ought also to separate out other variants as well, e.g. those cases in which myotonia *improves* with cold but becomes worse with warmth. Ravin (1939) reported such a case and also cited a case of Nylin's. D'Antona (1926) examined a patient affected by dystrophia myotonica whose tendon reflexes were abolished when he was in bed or in a warm room but which were present in a cold room. Ravin and Waring (1939) even distinguished between the paramyotonia congenita of Soelder and the paramyotonia of Eulenburg. Eulenburg (1916) in his second paper on paramyotonia stated that there was a near relationship between paramyotonia and myotonia congenita. Eulenburg (1916) stated that the stiffness *nearly* always resulted from a cold temperature. We deduce from this, then, that the myotonia *sometimes* arose independently of cold; that is, the condition was one of ordinary myotonia.

There are also cases in which myotonia actually increases instead of decreasing, as the result of repeated movements, called "myotonia paradoxa" by Jendrassik (cf. Weichmann, 1883; Bernhardt, 1887; Wichman, 1897; Stiefler, 1915; Hibner, 1917; and d'Antona, 1926). A brother of Hübner's case was diagnosed by Oppenheim as myotonia congenita. The patient himself had in addition to his myotonia, paramyotonia at times and a myopathic facies. T. Cohn (1904), Curschmann and Fürnrohr (1907) and Stattmüller (1923) also reported cases in which the myotonia either came on or was increased by repeated voluntary movements (cited by Franceschetti, Klein and Walthard, 1947).

We consider, therefore, that these minor variants, including paramyotonia, should all be considered one and the same disease.

SUMMARY

Since we wrote ten years ago stating that myotonia congenita and dystrophia myotonica were identical, the former being merely an early stage of the latter, several articles have been published supporting our conclusions, but there have also been writers such as Julia Bell, Franceschetti, Klein and Walthard, as well as Thomasen, who have disagreed.

These critics believe that a patient with myotonia will show one of two "typical" syndromes. In the first (myotonia congenita) the myotonia comes on from birth or early infancy and is widespread in its muscular distribution; there is hypertrophy of muscles; the patient preserves his reflexes and there is no wasting or weakness, no cataract and no testicular atrophy. Moreover, some other members of the family will be similarly affected.

In the second "typical" syndrome, however, 75 per cent are thought to be first affected only after the age of 15; myotonia occurs over restricted areas; marked wasting and weakness occur in a characteristic distribution and cataract and testicular atrophy occur. Some mention an asthenic build in dystrophia myotonica as against a pyknic one in myotonia congenita, and it is said by some that cataract always occurs in the former. Some members of the family are said to be affected while others entirely escape.

We agree that if there really were too clear-cut typical syndromes as described, which bred true in different pedigrees, then such conclusions would be valid.

We have shown, however, that the *typical* case of myotonia does not belong to either of these two syndromes but is intermediate between the two. The apparent case of myotonia congenita is found in time to develop symptoms of dystrophia myotonica. The case of dystrophia myotonica, on the other hand, frequently gives a history of symptoms said to be characteristic only of myotonia congenita, such as onset in infancy, pyknic build, hypertrophy and generalized myotonia.

Moreover, many members of such pedigrees present incomplete or mild clinical pictures, thus making it difficult for geneticists to draw any conclusions regarding the mode of hereditary transmission.

One of the chief arguments in favour of our view is that cases of "myotonia congenita" and cases of "dystrophia myotonica" frequently occur in the same pedigrees. This happened even in the original Thomsen family.

More complete investigation of the individual and of the family extended over a number of years have led to myotonia congenita being diagnosed less and less frequently.

The reasons which have led to the view that myotonia congenita is a

separate disease have been as follows: (*a*) Many pedigrees of "myotonia congenita" were published before dystrophia myotonica had been described and before slit-lamp examination was used to detect cataract. Hence slight degrees of wasting, cataract, and testicular atrophy may have been missed. We refer to many cases diagnosed as Thomsen's disease but which had absent deep reflexes, wasting of muscles, etc. (*b*) Many cases were seen over only a short period, that is before wasting could have time to develop. (*c*) Examination of pedigrees were incomplete, and so relatives with dystrophia myotonica may have been missed. (*d*) Incomplete cases were classified as normal, although many of these would in time be expected to develop definite symptoms of dystrophia myotonica. (*e*) There is a tendency in certain stocks for the myotonic stage to last unduly long without wasting occurring, but this does not constitute a different disease, for some wasting does occur in time, and in some members of the pedigree typical signs of dystrophia myotonica are very frequently found.

We have also discussed the condition known as paramyotonia and given our reasons for supposing that it, too, is merely a variant of dystrophia myotonica.

We see no reason for altering our opinion expressed in 1939 that the disease in whatever form should in future be called Thomsen's disease.

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THE EFFECT OF HEAD POSTURE ON THE MANOMETRICS OF THE CEREBROSPINAL FLUID IN CERVICAL LESIONS: A NEW DIAGNOSTIC TEST[1]

BY

LAWRENCE KAPLAN and FOSTER KENNEDY

Compression of the jugular veins as a means of determining the patency of the spinal subarachnoid space during lumbar puncture has not varied technically since its introduction by Queckenstedt in 1916.

Several refinements have marked its application throughout the years. These include: the use of the wider 18-gauge needle; the substitution of water manometers for the mercury type; the practice of abdominal compression to confirm the position of the needle; and the adoption of a neck compression cuff to replace manual digital compression of the neck veins. The position or posture of the patient during the test has never been significantly altered. As a routine, the lateral supine position, with the thighs flexed on the abdomen and the head slightly flexed on the chest, has been adopted because it eases lumbar puncture through widened interspinous spaces. On occasion relaxation of this "embryonic" posture has been required by the rise in spinal fluid pressure produced by it in the tense or obese person.

It is the purpose of this report to introduce a modification of the Queckenstedt test—variation of head posture during manometric studies—which aids detection of early cervical cord compression not revealed by the original procedure as heretofore applied. The preliminary report of this new technique was made before the American Neurological Association one year ago on the basis of a few case reports. Elaboration and more complete evaluation of the test is now possible. The present report includes the study of 294 patients with a total of 341 tests.

The demonstration of spinal subarachnoid block by the Queckenstedt test has been a keystone in the diagnosis of cord-compressing lesions. Two types of experience with this test as previously performed, however, have been enigmas in the correlation of results with operative findings. One is the absence of any manometric block in a number of surgically confirmed compressing lesions. The other is the presence of what appears

[1] From the Neurological Division (Cornell) of Bellevue Hospital, New York City (Doctor Foster Kennedy, Director). Read before the International Neurological Congress, Paris, 1949.

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to be a complete manometric block with consistently normal spinal fluid protein contents.

Attempts to explain these discrepancies have appeared from time to time in the literature. Thus, Stookey, in 1927, reported the results of CSF manometric studies in 10 cases of chronic adhesive arachnoiditis simulating cord tumour. Complete subarachnoid block was revealed in 5 cases, and "almost complete" block in the other 5. *All* of the protein contents were reported to be normal, although half the examinations were for globulin alone. This variation from the previous experience of elevation of spinal fluid protein contents with increasing subarachnoid block was then explained by the surgical observation that, unlike tumours compressing the cord, arachnoiditis was not accompanied by engorgement and distension of the veins below the level of compression. These venous changes have been considered responsible for the changes in protein content by the simple process of transudation. Another explanation of the normal protein levels is tenable on the basis of the results we wish to report.

Pappen and Hurxthal, in 1934, reported a case of tumour of the spinal cord at the high thoracic level with a normal Queckenstedt test. It was their contention that manometric abnormalities occur only if the opening left by the tumour and cord is smaller than the bore of the spinal needle, on the basis that the flow of fluid through a larger opening cannot be measured through a smaller one. In 1943, Fleiss and Ingham accumulated a series of twenty suspected cord-compressing lesions treated surgically in the presence of perfectly normal manometric studies. Of the 20 cases, 10 showed extrinsic pathologic processes for which surgical intervention bore some hope of improvement. Of these 10 cases, 6 had definite space-occupying lesions, either neoplasm or herniated intervertebral disc. Of importance in this respect is the fact that the level of the lesion in these cases was cervical in 5 and thoracic in 1. Adhesive arachnoiditis accounted for the remaining 4 of the 10 surgically amenable lesions. The 10 cases without demonstrable extrinsic compressing processes showed either a normal-appearing spinal cord or cord atrophy. The application of the test to be described in a series such as this will become apparent.

Material

The technique of variation of head posture during the study of cerebrospinal fluid manometrics by lumbar puncture was applied to a series of 294 patients for a total of 341 punctures. Most of these patients were examined on the Neurological Division of Bellevue Hospital, New York City, although several cases from the Neurological Departments of the Veterans Hospital, Bronx, N.Y., and the New York Hospital were added

during recent months. Since the specificity of the test for certain cord-compressing lesions was originally in doubt, a wide variety of neurological disorders was studied, excluding only those cases in which lumbar puncture or the manometric test was unquestionably contra-indicated. The number of patients in each diagnostic group is listed in Table I.

TABLE I.—CLASSIFICATION OF CASES BY DIAGNOSIS

		No. of cases
1	Cervical cord lesions (compression suspected)	31
2	Convulsive disorders	29
3	Heredo-familial and degenerative brain disease	28
4	Syphilis (including neurosyphilis)	23
5	Psychoneurosis	21
6	Vascular disease of the brain	21
7	Herniated lumbar intervertebral discs	19
8	Multiple sclerosis	16
9	Radiculitis secondary to vertebral arthritis	14
10	Peripheral neuropathy	12
11	Post-traumatic cerebral syndrome	12
12	Brain tumour suspects	11
13	Parkinson's disease	10
14	Amyotrophic lateral sclerosis	7
15	Atypical facial pain	6
16	Syringomyelia	6
17	Thoracic and lumbar cord tumours	6
18	Myasthenia gravis	5
19	Muscular dystrophy	5
20	Trigeminal neuralgia	4
21	Subacute combined degeneration of cord	3
22	Herpes zoster	2
23	Huntington's chorea	1
24	Thalamic syndrome	1
25	Causalgia	1
	Total number of cases	294
	Total number of tests	341

TECHNIQUE

With the patient in the lateral supine position on either side, a lumbar puncture is performed with an 18-gauge needle at the L3–4 or L4–5 interspace. After successful puncture of the subarachnoid space, the position of the patient is re-checked. No more than 90 degrees of flexion of the thighs on the abdomen is necessary. The head is centred in relation to the trunk by placing a small pillow under the parietal surface next to the table. Two observers must be present, one for the sole purpose of managing the changes in head posture and compression of jugular veins.

Before manometric studies are begun, the head is placed in the "neutral" position, in line with the trunk or very slightly flexed. The

manometer is then attached and the initial pressure recorded. The rise in pressure with firm abdominal compression must first be estimated while the patient avoids straining or holding his breath. If a free connexion is established, the manometric response to manual jugular compression, bilaterally applied, is recorded. The head is then fully flexed while the observer's hands maintain contact without pressure on the neck structures. In this position, the jugular compression test is repeated and the results noted. Finally, the head is fully extended on the neck, and the test repeated for the third time. The thoracic cage should be immobile during these manipulations. In each of the head postures, abdominal compression is done after jugular compression to assure free connexion. The purpose of the test is, of course, to determine whether subarachnoid block, as manifested by pressure studies, exists in only one, two, or all positions of the head. More recently, many of the tests have included additional manipulation of the head and neck into the laterally flexed and laterally rotated positions. Attention to the following details is necessary if the test is to be considered reliable:

(1) *Mid-line puncture.*—A mid-line puncture is required for proper penetration of the lumbar subarachnoid space. The bevelled edge of the needle will help this. Initially, the needle is inserted with the bevel placed caudad. If the needle tends to deviate laterally, this may be corrected during further progress of the needle by use of the sheering action of the bevel. As the dura is approached, the bevel is turned laterally so that the cutting edge may penetrate the dura in the direction of its fibres. After a free flow of spinal fluid is obtained, the bevel is again turned caudad, this usually resulting in a very brisk flow since the bevel opening is now between the roots instead of against them.

(2) *Abdominal compression.*—This part of the test must be done repeatedly with each change of head posture since it assures a free fluid connexion. If the needle puncture is not well fixed, manipulation of the head, even without other motion of the body, may exert enough traction on dura and/or roots to cause displacement of the needle and bizarre results, hard to interpret.

(3) *Manual jugular compression.*—The observer whose task is jugular compression should be trained in locating the veins of the neck posterolateral to the carotid pulses and in the technique of compression, consisting of gently increasing occlusion of the neck veins between the palmar surfaces of the distal digits of both hands and the transverse processes and paravertebral tissues of the cervical spine. The signs of successful compression, i.e. erythema of the face, engorgement of the facial and conjunctival vessels, and the complaint of "fullness in the head," should be confirmed if a manometric rise does not follow adequate compression.

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The use of an inflated compression cuff around the neck as a more uniform substitution for manual compression was discontinued after both procedures had been applied in the earlier cases. It was found that the inflated posterior portion of the cuff acted as a brace to prevent full extension of the head on the neck. In one case in point (No. 8) a complete manometric block was demonstrated by manual compression, with the head in extension, and no block by cuff compression in the same position, though the degree of venous engorgement from clinical signs was the same. It was found that full extension of the head with the cuff applied was 20–25 degrees less than without the cuff.

(4) *Oversensitive carotid sinus.*—Two cases of sensitive carotid sinus, accidentally encountered, showed abnormal manometric studies of which one must be aware. In each of these cases, no previous symptoms referable to sinus sensitivity had been experienced. In both the reactions occurred with gentle, incomplete compression of the neck structures. In one, the clinical response was of the "vagal" type with marked bradycardia and syncopal feelings. In the other, the response was "cerebral" in type with loss of consciousness, clonic movements of the extremities, and no significant change in pulse-rate or blood-pressure. In both, the manometric response of the spinal fluid was the same, viz. slight rise of pressure with gentle jugular compression, then sudden cessation of the rise, onset of symptoms and, as soon as compression was released, a paradoxical rapid and significant rise of pressure, then followed by the usual decline. These changes are undoubtedly related to the effect of the sensitive carotid mechanism on cerebral vascular structures and are being studied further. Nevertheless, they must be avoided and have no relation to variations of head posture.

(5) *Contra-indications.*—Though manipulation of the head and neck has become an integral part of the complete neurological examination in suspected cervical lesions as a means of demonstrating muscle spasm, limitation of motion, and specific production of pain, there are two relative contra-indications to the extreme changes in head posture required by the proposed technique: in any recent acute cervical spine injury, and in any suspected high cervical-foramen magnum lesion, in which additional compression following manipulation of the head may interfere with vital medullary centre functions.

Results

Of the total series of 294 patients tested in the aforementioned manner for the response of CSF manometrics to variations in head posture, 31 had clinical diagnoses of cord-compressing lesions in the cervical region (Table I). 3 of these 31 cases showed complete subarachnoid block un-

TABLE II

Pt.	*Age*	*Sex*	*Duration Illness*	*Roentgenograms Arthritis*	*Nar. Disc*	*Ext.*	*Results of Test Neut.*	*Flex.*	*CSF Protein*	*Surgical Findings Lesion*	*Level*	*Rept.*
1–HZ	57	M	7 yrs.	+	+	CB	Nl.	Nl.	54–78	Large exostosis; atrophic cord; arachnoiditis	C5–6	NI
2–MC	59	F	13 mos.	+	—	CB	Nl.	Nl.	39	Arachnoiditis	C4–7	NI
3–FA	64	M	6 mos.	—	+	CB	PB	PB	127	Adhesive arachnoiditis	CD–DI	—
4–HT	73	M	1 yr.	+	+	CB	Nl.	Nl.	87	Large exostosis	C5–6	NI
5–	49	M	6 mos.	—	—	NI	Nl.	CB	110	Not done	—	—
6–AM	57	M	17 days	+	—	CB in lat. flex. 43 and rotation				Not done	C6–7	NI
7–AS	40	M	3 yrs.	+	—	CB	Nl.	Nl.	72	Large exostosis	C5–6	—
8–OC	22	F	2 mos.	—	+	PB	Nl.	Nl.	43	Herniated disc left	C6–7	NI
9–WW	45	M	2 days	+	+	CB	Nl.	Nl.	45	Herniated disc; cord contusion	C5–6	NI
10–LF	56	M	2 yrs.	—	—	CB	Nl.	Nl.	39	Exostosis	C5–6	—
11–WL	50	M	2 yrs.	+	—	PB	Nl.	Nl.	116	Not done	C5–7	—
12–LS	42	M	4 mos.	—	—	CB	Nl.	Nl.	96	Not done	C4–6	—

changed by variation of head posture. 16 had normal tests in all positions. The remaining 12 showed abnormalities in one position, but not in the others. It is this latter group which forms the basis of this report.

Table II lists the significant data in each of the 12 cases showing manometric abnormalities only with changes of head posture. The series included 10 men and 2 women, this incidence bearing some relation, perhaps, to the ætiological factors. The ages of the patients varied from 22 to 73; 9 of the 12 were in the fifth and sixth decade group. The duration of symptoms prior to the performance of the test varied from two days to seven years, although the majority of patients had been ill for four to twenty-four months. The results of the 12 abnormal tests are classified in Table III. 4 of the 12 cases were treated non-operatively.

TABLE III

(A)	Complete block in extension, normal results in neutral and flexion	7 cases
(B)	Partial block in extension, normal results in neutral and flexion	2 cases
(C)	Complete block in extension, partial block in neutral and flexion	1 case
(D)	Complete block in left lateral flexion and rotation in slight extension, normal in other positions	1 case
(E)	Complete block in flexion, normal results in neutral and extension	1 case

Exploratory laminectomy was performed on 8, and extrinsic cord lesions in the cervical region confirmed surgically in each. Of these 8 surgically treated cases, 6 were in Group A (Table III), 1 in Group B, and 1 in Group C. The lesions, and their respective levels, discovered at operation, are listed in Table II. No tumours were found; compressing exotoses of the cervical spine (arthritic or calcified disc protrusions) at the level of C5–6 were found in 4 cases; herniated discs at C6–7 and C5–6 were found in 2, and adhesive arachnoiditis of the middle and lower cervical regions in 2. The fact that 5 of the 8 operatively demonstrated lesions were specifically localized to the C5–6 level provides a mechanical explanation for the production of subarachnoid block by placing the head in extension. The pivotal point for movement of the cervical spine on an immobile thoracic spine is in most cases at this level.

Of the 16 cases of cervical lesions showing normal tests, 7 had exploratory laminectomies. 6 of these had no demonstrable lesion at operation and 1 had a slight filmy cervical arachnoiditis. Partial or complete manometric block unrelated to head posture was found in 6 of the remaining 259 patients with neurological diseases not primarily involving the cervical cord. Cord tumours in the thoracic or lumbar region accounted for these.

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Normal tests were found without exception in each of the remaining 253 cases.

In the group of 12 cases with abnormal tests on postural variation of the head, an analysis of spinal fluid protein levels revealed the following: 6 of the 12 cases had normal protein levels; 3 had slight protein elevations (less than 100 mg. per cent); and 3 had moderate elevations (over 100 mg. per cent). The discrepancy between subarachnoid block and protein elevation in these cases is now explained on the basis of "intermittency" of block depending upon the position of the head and neck.

Pantopaque myelograms were performed in only 4 of the 12 cases before surgical intervention. In each of these, characteristic findings were noted. With the head in the hyperextended position required for cervical myelography, there was complete stoppage of the pantopaque at the level of the lesion. Then, as the head was slowly flexed, the pantopaque began to trickle down the lateral aspects of the defect, outlining mid-line protrusions rather well. With further flexion, it was possible to move all the pantopaque above the level of the lesion. It was then possible to pool the pantopaque above the level by repeat hyperextension of the neck despite reverse tilting of the table to the point where the pantopaque would normally flow by gravity to the lower lumbar subarachnoid sac. Flexion of the head with the body in this position would then result in a sudden release of pantopaque down past the defect. In this way, myelography confirmed the effect of head posture on blockage of the cervical subarachnoid space.

In 11 of the 12 cases, manometric studies were repeated two or more times on separate occasions. Identical abnormalities were constantly demonstrated. In 5 cases, the test was repeated within six weeks after laminectomy; in 1 other case it was repeated within the week after spontaneous remission of the typical clinical syndrome of a left C6–7 disc protrusion. All 6 of these subsequent tests revealed normal results. In those cases with cervical spine exostoses, the surgical treatment consisted only of decompression and section of dentate ligaments, without any attempts at removal of the projecting bone. The traumatizing effect of such excisions of ventral exostoses has been well appreciated in the past. There was no specific correlation of roentgenographic abnormalities of the cervical spine with the abnormal tests or the responsible lesion. Normal roentgenograms were reported in 4 cases, and hypertrophic changes with disc narrowing in 8.

Summary

A new diagnostic test is reported, helpful in the detection of early compression of the lower cervical portion of the spinal cord. This varies

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from the original Queckenstedt test by the addition of changes in head posture during jugular compression. "Intermittency" of spinal subarachnoid block dependent upon the flexed or extended position of the head and neck has been found in 12 cases having normal spinal fluid dynamics by the older technique. The phenomenon of "intermittent" block is pathological—not physiological, since normal tests were encountered in all 253 patients with neurological disorders without suspicion of cord compression. The technique of the test, its sources of error, and an analysis of the abnormal results are reviewed.

Absence of manometric block in a certain proportion of cervical cord compressing lesions and the presence of a block when the CSF protein content is normal are two previously disturbing situations which may be clarified by this revised procedure.

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ANTEROLATERAL CORDOTOMY: RESULTS, COMPLICATIONS AND CAUSES OF FAILURE[1]

BY

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TRANSECTION of the spinal pain pathway, on the basis of Spiller's observation in 1905, was first carried out by Martin at Spiller's (1912) suggestion thirty-eight years ago. During this period a number of excellent descriptions of the surgical procedure have been published, but attempts at long-range assessment of the value of the operation—its risks and complications, as well as the proportional incidence of early and late failures—have been few. Among those who have tried to find the answer to these questions are Banzet (1927), Foerster and Gagel (1932), the Russian Babtchine (1936), Kahn and Peet (1948) and Hyndman and his collaborators (1939, 1943) in this country, and Sjöqvist (1949) in Sweden. Even in these reports, however, there are few prolonged observations or complete neurological studies.

The present time is, we think, a particularly appropriate one to take stock, as numerous surgeons have become disheartened by their failures to obtain and maintain an adequate level of analgesia. In addition, it has become apparent that what is often reported as complete analgesia to cutaneous pin-pricks is, in reality, only a high degree of hypalgesia. Unfortunately, it is not yet generally known that this degree of denervation may permit full sensation of the original pain. Failure to appreciate this fact has led to an increasing tendency to discount the true value of anterolateral cordotomy, and to substitute such a mutilating procedure as bilateral frontal leucotomy for relief of pain in tabetic crises, lesions of the cauda equina, causalgia, phantom limb, and advanced carcinoma of the abdominal and pelvic organs (Freeman and Watts, 1948; Hawkes and Gotten, 1948; Hamilton and Hayes, 1949). In view of the fact that leucotomy seems to be followed by a more obvious degree of inertia when performed for relief of pain than in the treatment of psychiatric disorders, and because it is followed by other serious psychic disturbances (Hoffman, 1949), this substitution can hardly be justified provided effective relief can be obtained by simple transection of pain tracts.

[1] From the Neurosurgical Service of the Massachusetts General Hospital, Boston, Massachusetts. A preliminary account of this work was given before the Harvey Cushing Society in New Haven in June 1949, and the full paper was read before the Society of British Neurosurgeons in Manchester, 1950.

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Material for Study

Owing to a long-standing interest in both somatic and visceral pain, and thanks to the co-operation of the hospital staff, we have had an unusual opportunity to investigate the effectiveness of cordotomy. We have chosen for statistical review all the anterolateral tractotomies performed from 1936 to 1948 inclusive. The operations were done by Drs. W. J. Mixter, J. S. Hodgson, J. J. Michelsen, various residents, and the authors of this paper. Only the case records of 1944 are not included, because all the authors were then in military service and many of the routine observations were not made. Our statistics over this twelve-year period are based on 241 cordotomies performed on 210 patients. In 126 the operation was unilateral, in 84 bilateral. 19 of the bilateral tractotomies were performed in two stages. In 12 individuals secondary cordotomies were subsequently carried out on the original side.

Table I summarizes the varieties of conditions associated with severe

Table I.—Pathological Classification of Causes of Persistent Intractable Pain in Individuals Submitted to Anterolateral Cordotomy

	No of patients
Malignant tumours:	
Breast	13
Lung	9
Kidney	4
Bladder	8
Colon and rectum	30
Prostate and testicle	8
Uterus, vagina, and vulva	40
Bone	16
Miscellaneous	17
Spinal trauma and disease:	
Paraplegia	8
Arachnoiditis	9
Tabes	7
Herpes zoster	3
Miscellaneous	8
Neuralgias:	
Post-operative	3
Phantom limb	10
Amputation stump	9
Miscellaneous:	8
Total	210

persistent pain for which this procedure was done. Of this group we were able to follow up the results in 100 patients for periods of two months to eleven years. In addition we were able to arrange for the return for

special extensive examination of 20 patients in whom a unilateral upper thoracic or cervical cordotomy had been performed five months to ten years previously.

Operative Technique

Anæsthesia.—We have insisted on the necessity of establishing the level of sensory loss at the time of operation. Time and again what has appeared to be a radical transection of the anterolateral column has been found to abolish appreciation of pain no higher than the lowest thoracic dermatomes. It usually takes a second or even a third deeper incision to raise the sensory level to mid-thoracic or higher segments. Consequently, it is of vital importance to perform the operation under local anæsthesia. Apprehensive individuals may have the primary infiltration of procaine supplemented by a light dose of intravenous sodium pentothal and nitrous oxide anæsthesia, so that they may be kept asleep during the critical period while the cord is mobilized and incised. It is essential that the patient be given time to regain full consciousness. If recovery is unduly prolonged, it may possibly be accelerated by the intravenous use of metrazol (100 mg.), benzedrine sulfate (10 mg.), or picrotoxin (1 to 10 mg.), but with patience this is usually unnecessary. The patient should always be coached pre-operatively on the method of testing and the vital importance of his co-operating and differentiating between the sharp point of a needle or the nip of a tongue or towel clip and the dull sensation of touch which he will feel in the analgesic zone. In our experience, about one-third of the patients have been unable to tolerate this operation under local, or became unmanageable when awakening from the combined pentothal-gas narcosis. The proportion of failures in this group amounted to 27 per cent, in contrast to 11 per cent in those in whom accurate verification of a satisfactory level was demonstrated on the table.

Technique of tractotomy.—Our method of transecting the pain pathway in the upper thoracic cord is substantially that described by Grant (1930), Kahn and Peet (1948), and Hyndman and Van Epps (1939). For pain below the mid-thoracic level, our incision is made over the upper three thoracic vertebræ. It is necessary to remove only a single lamina, plus the lower half of the one above and the upper half of the one below. The dural attachment of a single fascicle of the dentate ligament is cut on each side, as recommended by Kahn and Peet, to permit maximal rotation of the cord. The dentate on the side of the incision is then grasped with a fine snap close to its attachment to the cord. A single posterior root is cut if this will facilitate the exposure. Brief application of a cotton pledget soaked in 2 per cent procaine will eliminate pain when this is done. The cord may be rotated nearly 90 degrees: or alternatively, in order to avoid rotational distortion, one may gain additional space by removing most of the pedicle just lateral to the proposed site of incision into the cord. We then use the broken-off pointed tip of a No. 11 Bard-Parker knife blade, which projects 5 mm. from the jaws of a small hæmostat, to make the primary incision in the cord in the usual upper thoracic cordotomy in an adult patient (where the average transverse diameter of the cord averages 10 mm. ± 1). At higher levels, C1 and C5, where the respective diameters of the cord average 12·5 and 1·5 ± 1 mm., the blade should project to a correspondingly greater extent. This is used to sever the pia mater and to make the primary incision on a transverse plane just anterior to the attachment of the dentate ligament. The curved cordotomy hook[1] is then inserted into the incision and swept ventro-medially until its tip emerges at least 2 mm. ventro-medial to the

[1] The Frazier cordotomy hook in use at this hospital is a fine half-round hook, 4 mm. in diameter, fixed at right angles on the end of a delicate handle. By this means the fibres to be cut are elevated and then severed on the hook by a fine sharp knife.

line of attachment of the anterior spinal roots. To secure a maximally high level of analgesia we deliberately attempt to transact virtually the entire anterior quadrant of the cord, with due precautions not to injure the anterior spinal artery (fig. 1). As stated above, the first incision is rarely deep enough, and several deeper insertions of the hook may be required in order to obtain a level of analgesia up to the nipple line. If the tracts are to be cut bilaterally, two entire laminæ are removed with parts of the ones above and below. The incisions in the cord are made 2 to 4 cm. apart.

In order to raise the level of analgesia above the nipple line we have usually made the transection at the first or second cervical level to desensitize the upper extremity, or even in the medulla, as described by Schwartz and O'Leary (1941). The first patient to survive this high operation, reported by White (1941), had a complicating ataxia for a number of months. To avoid this in subsequent cases, we have dropped the point of section below the level of the obex, which obviates the chance of injuring the vestibular nuclei or restiform body. This operation has now been carried out by two of us in 6 further patients without complications, save for 2 fatalities in individuals with advanced malignant disease of the neck and œsophagus. It has, however, proved impossible to maintain an analgesic level above the third cervical segment. This initial level has frequently fallen to the clavicle, and once considerably lower.

Method of testing for pain.—Most surgeons are unaware of the fact that the loss of appreciation of single pricks or the continuous scratch of a needle point as a sharp or pointed sensation does not prove total analgesia. Testing in this way may indicate only a high degree of hypalgesia. We also were unaware of this fact prior to 1946. In such instances after cordotomy stimulation with a pin or other painful agent may cause a disagreeable feeling not described as pain, but which the patient can distinguish from a normally painless stimulus. At times a disagreeable or painful quality may appear only after multiple rapid pricks with a sharp point (five to ten rapidly repeated pricks of the pin over a centimetre square of skin). In such patients pain, which may or may not be similar to that present preoperatively, may come on after operation. We were at first uncertain whether or not repetition of the anterolateral cordotomy would eliminate either the spontaneous complaint of pain or the discomfort on stimulation. We considered the possibility that other pathways in the cord outside the contralateral anterolateral quadrant might transmit such stimuli. One such patient, for example, stated that a pin-point or a hot or an iced tube caused an electric shock or a burning, peculiar feeling coming on at once at the site of stimulus. However, the repetition of her thoracic cordotomy two segments higher was followed by elimination of her spontaneous pain and absence of the discomfort on objective testing. In other patients, who complain of recurrent pain despite an adequate upper level of analgesia, thorough examination may reveal residual sensory islands in which pin-prick or continuous pin scratch is sharp or unpleasant. In one such patient the only area of skin in which such pain could be elicited was limited to about 10 sq. cm., yet repetition of the cordotomy was followed by relief of all pain and analgesia in that zone as well.

It is apparent that exhaustive testing is required to establish the adequacy of the denervation. Some astute patients learn to distinguish the point from the head of the pin in an analgesic zone merely by the greater area touched by the head of the pin. Accordingly, in order to avoid confusion, we test by comparing the response to a stimulus consisting of either (1) a finger-tip alone or (2) that plus the point of a pin projecting beyond the finger-tip. These two stimuli should be indistinguishable in an effectively cordotomized area. If they can be differentiated and the stimulus with the pin is more disagreeable, our current impression is that a subsequent deeper cordotomy will stop the pain. At least, this has been the outcome in 4 such cases.

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Results

Table II, A, shows that 196 operations or 81 per cent of the total gave

Table II.—Effect of Anterolateral Cordotomy on Pain in 210 Patients*

		No. ops.	per cent
A.	*Early results following 241 operations (up to one month post-operatively):*		
	Analgesia and complete relief of original pain ...	196	81
	Partial return of pain (insufficient to require narcotics)	23	10
	Failure to relieve pain	22	9
B.	*Later results of 100 of these operations in patients who had early complete relief (two months or more post-operatively):*		
	Effective relief, or no medication required (average 15 mos.)	63	63
	Partial relief (average 7 mos.)	18	18
	Failure (average 7 mos.)	19	19
C.	*Late results of unilateral cordotomy in 20 patients submitted to detailed follow-up studies five months to ten years after operation:*		
	Effective relief, or no medication required (average 46 mos.)	15	75
	Partial relief (average 40 mos.)	2	10
	Failure (average 63 mos.)	3	15

*These statistics apply to relief of the original pain. For data on subsequent appearance of pain after unilateral cordotomy on opposite side.

complete relief of the original pain up to the time of the patient's discharge from the hospital. Partial return of pain, but insufficient to require further administration of narcotics, occurred in 10 per cent, while 9 per cent resulted in less satisfactory or no relief. Of the 157 operations first performed on one side only, 89 were in patients who had malignant disease of the torso. In this group there was an early appearance (within two months) of pain on the opposite side in 31, or 35 per cent. In an additional 8 of 20 individuals in this latter group who were followed for over two months, pain later appeared on the opposite side. In 39 sufferers from malignant disease, or 44 per cent of the total observed, unilateral cordotomy was therefore insufficient to provide lasting relief. This sequela was much less frequent in non-malignant conditions of the torso, where it only appeared 4 times in 36 patients, 28 of whom were followed for two or more months. Cross-over of pain never occurred in patients with disease confined to a single extremity.

The pain of advanced carcinoma may be so severe on one side that lesser contralateral discomfort is masked. Nevertheless, this may give rise to severe pain just as soon as the predominant complaint has been eliminated. This is also true of pain in other varieties of visceral disease arising from mid-line organs such as the heart and pancreas. Just as soon as the pain on the predominant side has been relieved by sympathectomy or splanchnicectomy it is likely to appear on the opposite side,

because there organs have bilateral innervation. Transference of pain to the side originally uninvolved is most likely to occur in carcinoma of the uterus, bladder, or prostate[1], where lymphatic spread so often involves the lumbo-sacral plexuses on both sides. Not infrequently, however, unilateral cordotomy gives complete and lasting relief of pain initially unilateral. Conversely, in 3 cases in which the pain was bilateral from the beginning, very satisfactory relief has followed unilateral incision. 2 of these patients suffered from tabetic crises and one from malignant disease. The latter was completely freed of her original bilateral anorectal pain and all other pain until her abrupt demise seven months after the cordotomy. Of the patients with tabetic pain, one continues so nearly free of his gastric crises after eighteen months that he has lost no time from work and gained 50 lb. in weight; the other, with lightning pains in both the lower limbs, remained greatly relieved at thirteen months.

Prolonged follow-up of the early successful cases is of particular importance, as there is always the possibility that the initial satisfactory level of complete analgesia may recede many segments or be replaced in a patchy manner or throughout by a variable degree of hypalgesia. As an extreme example, a patient who was effectively relieved of pain in the stump of an amputated thigh for over a year had a recurrence following a late drop of the sensory level. After intervals of over two months, 63 per cent of 100 operations continued to give complete relief on the denervated side, 18 per cent partial improvement, and 19 per cent no benefit (Table II, B).

Special examinations were obtained in 20 patients after post-operative periods ranging from five months to ten years. The observations in 14 were made over two years post-operatively. These include all of our patients whose return for such study we were able to arrange and represent no other special selection. Many of these late survivors were amputees who formerly suffered from painful limb phantoms or major neuralgia in their stumps. 15, or 75 per cent, maintained a satisfactory degree of relief. There were 2 who required small amounts of medication and 3 were failures. These are summarized in Table II, C. The causes of early and late failures will be analysed below. It is possible that this series is unduly weighted with our successes. We know of at least 2 other cases in which the operation failed to give permanent relief, but we were unable to persuade the patients to return for examination.

[1] One patient in the advanced stage of carcinoma of the prostate with bony pelvic metastases had complained of only unilateral pain. The day after its operative relief he complained that it had shifted in full severity to the opposite side, necessitating a secondary contralateral tractotomy a week later.

Complications

The operative mortality amounted to 4 per cent in this series of 210 patients, 168 of whom were operated upon in the advanced stages of malignant disease (Table IIIA). Of these 9 deaths attributed to the opera-

Table IIIA.—Complications Persisting to Time of Discharge in 210 Patients

	Operative Deaths	*Bladder*	*Bowel*	*Incisional Radicular Pain*	*Motor Weakness*	*Case Total*
Unilateral* ...	3	5%	2%	2%	4%	126
Bilateral, 1-stage	5	29%	5%	2%	8%	65
Bilateral, 2-stage	1	16%	10%	0%	10%	19
Total	9	13%	4%	1%	5%	210

*10 of these, with incomplete analgesia and continued pain, were submitted to secondary tractotomy without any complications.

Table IIIB.—Comparison of Complications following Unilateral Thoracic and High Cervical Cordotomy

	Operative Deaths	*Bladder*	*Bowel*	*Incisional Radicular Pain*	*Motor Weakness*	*Case Total*
Thoracic ...	0	2%	2%	1%	4%	92
Cervical ...	3	12%	3%	3%	3%	34

tion, 2 were caused by immediate circulatory and respiratory failure, 4 by atelectasis and pneumonia, and 1 of each by pulmonary embolism, cerebral contusion following a fall, and pyelonephritis secondary to prolonged catheterization. 13 other deaths occurred in the hospital from advanced malignant disease. These included exsanguination from erosion of large blood vessels by tumour, uræmia from ureteral obstruction, and generalized cachexia. It is evident from Table IIIB that the incidence of deaths is somewhat greater after high cervical tractotomies than after those carried out in the upper thoracic portion of the spinal cord.

The most generally feared sequelæ of cordotomy are disturbance in control of the bladder and muscular weakness. The post-operative incidence of these complications and others which are less commonly recognized are summarized in Table IIIB. In all our cases the post-operative difficulty consisted of an atonic bladder with retention and rarely lead to urinary tract infection. Much less frequently other observers have found relaxation of the vesical sphincter and annoying dribbling. During the first week after operation retention is so common that we routinely insert a Foley catheter in the operating room. Tidal drainage may be used and is essential if spontaneous voiding fails to start within a week. However, a cystometrogram made at this time, when the patient is up, usually shows active reflex contractions with sensation of fullness at volumes over 300 c.c. The catheter is then removed, but reinserted on one or more occasions

after the return of spontaneous micturition to determine the amount of residual urine. Catheterization should be continued once or twice a day if this remains excessive or the inlying catheter replaced for a further period if there is any serious retention. Only rarely has it been necessary to resort to protracted tidal drainage for bladder re-training, but so much can be accomplished by this that prolonged impairment of voluntary control is now a rare problem. Following a unilateral upper thoracic tractotomy only 2 per cent of our patients have continued to have difficulty and have required catheterization beyond the time of discharge from the hospital. In the individuals who had prolonged retention there was nearly always some pre-existent mechanical obstruction or impairment in the emptying of the bladder. Following unilateral high cervical cordotomy, however, the incidence of bladder complications appears to be significantly raised (12 per cent—Table IIIB). After bilateral cordotomy performed at one stage, the incidence of this complication rose to 29 per cent, but when both anterolateral columns had been transected in two stages a week or more apart it was reduced to 16 per cent. We have not found prostigmine or other cholinergic drugs of much value. A few patients, particularly elderly males with slight degrees of prostatic enlargement and others with involvement of the sacral nerves, have required transurethral excision of tissue at the bladder neck. In the special group of 20 patients reviewed between five months and ten years post-operatively, all had adequate control of urination.

Temporary inability to control the anal sphincter with fæcal incontinence was observed much less frequently and was rarely a cause of prolonged complaint. Prolonged relaxation or inability to distinguish between gas and fæces led to soiling of the clothes at times in 8 patients, 3 of whom had been previously subjected to subarachnoid injection of alcohol.

Obvious weakness of the leg on the side of the cordotomy was a cause of complaint after 4 per cent of unilateral operations, and twice as often after bilateral tractotomy. It was fortunately not a problem in any of the 19 individuals who had the operation performed for painful leg phantoms or stump neuralgia, and it continued to be a source of complaint in only a single patient examined after five months. This man, with degenerative arthritis of the hip, required support of a cane in walking, but had so much disease in the hip on the side of the tractotomy that it was difficult to estimate the degree of residual weakness. However, if strength of individual muscles is measured quantitatively and compared on the two sides after unilateral operations, a definite weakness will nearly always be found during the first few weeks on the side of the tractotomy.

On the rare occasions when more severe degrees of paresis are present,

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it is our opinion that this may be caused by injury to the blood supply of the pyramidal tract. Suh and Alexander (1939) have shown that this is supplied by branches from the anterior spinal artery which pass through the base of the anterolateral quadrant. If one of these is injured, œdema or necrosis may result in a portion of the lateral cortico-spinal tract. Observations made in the course of deliberate section of this tract, as practised by Putnam (1940) and Ebin (1949) in their operations for Parkinson's disease, have demonstrated that interruption must be extensive to produce serious weakness. Fig. 2 is the photomicrograph of the spinal cord in a woman who died, eighteen days after anterolateral cordotomy, from uræmia secondary to ureteral obstruction by carcinoma originating in the cervix uteri. While the incision appears to have been made too far dorsally, she was relieved of pain and had no noticeable weakness of her leg.

Changes in reflexes observed five months or more after operation were slight. 10 of the 20 individuals tested had demonstrable evidence of mild neurological abnormality: a reduction in abdominal and cremasteric reflexes, a slight but definite increase in the deep tendon-jerks, or a positive Babinski response. Only a single patient, with degenerative arthritis of the hip, complained of any decrease in walking ability.

Other post-operative complications consisted of radicular pain, reduced sexual function, and various forms of dysæsthesia and allachæsthesia. The radicular pain is felt as a band of pain or disagreeable sensation radiating to one or both sides along the course of the spinal nerves at the segmental level of the incision. This usually disappears in the course of a few weeks, but one patient examined ten years after operation claimed that she was disturbed by the sensation for three years before it finally vanished.

Masculine complaints on the score of reduced sexual potency or gratification range all the way from complete impotence to the statement that the "voluptuous sensation of intercourse is lost" (Kahn and Peet, 1948). In contrast, one of our patients, aged 66 years, boasted that he enjoyed normal intercourse the night he left the hospital after a unilateral cordotomy. Any severe operation may reduce sexual activity, but in general in our patients with cordotomy for non-fatal disease there has been a gradual return of any lost function over a period of weeks to years. Women also may notice some reduction or absence of genital activity and pleasurable sensation during intercourse. In our group there were only three vigorous married women to question after unilateral cordotomy. Two had essentially normal sexual sensation and one of these became pregnant. A third girl, despite unimpaired libido, complained of absence of all erotic sensation in the genial region.

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Eight patients have complained of dysæsthesias in the hypalgesic or analgesic areas. These have consisted of a wide variety of subjective sensory disturbances: sensation of "pins and needles" (3 cases), "electric shock-like pain" in leg (2 cases), "rawness" over great trochanter (2 cases), "burning" in foot (1 case), and disagreeable "numbness" (1 case). The latter complaint was difficult to evaluate, as this man was effectively relieved of his painful phantom leg, but deeply resented the fact that he could stick pins through his analgesic skin without normal sensation. The patient with residual burning sensation in her foot was a psychoneurotic in whom evaluation was difficult, but the others seemed to be relatively stable from an emotional standpoint.

Allachæsthesia, the reference of sensation to other areas, is a curious misinterpretation of the origin of sensory stimuli. As an example of this phenomenon, a woman with a shoulder disarticulation and a painful phantom of her arm which seemed to be drawn up in a cramped position behind her back had been relieved of all discomfort for six months following anterolateral cordotomy at the first cervical level. The phantom unfortunately reappeared because her level of total analgesia fell, with the appearance of islands of disagreeable sensation over the trunk and leg. Rapid repetitive pricking with a pin in these areas was perceived as peculiarly disagreeable, rather than normally painful, but this sensation was referred to her shoulder stump and phantom arm. Another woman with multiple bony metastases from carcinoma of the breast, which caused left lower abdominal and leg pain, was effectively relieved of this discomfort. Her analgesia level after cordotomy reached the mid-thorax, but she was able to identify repeated pin-pricks below this level by a disagreeable sensation referred to her axilla. A number of other peculiar misinterpretations of the source and type of sensory stimuli have been observed in this special group of 20 patients, usually when analgesia was incomplete. These may be summarized as follows:

(1) Rapid pin-pricks and a variety of other stimuli over the analgesic half of the thorax and abdomen produced pain in corresponding areas on the normal side in 4 patients.

(2) Squeezing the testicle on the analgesic side led to reference of pain to the opposite groin or to both buttocks in 2 patients.

(3) Pulling pubic hair on the analgesic side caused disagreeable sensation in the opposite hip.

(4) Pain may be referred to regions higher up on the analgesic side than the point stimulated, e.g. compression of the Achilles tendon led to painful sensation in the analgesic hip; fast repeated pin-pricks of an amputation stump of the right thigh evoked pain just to the right of the umbilicus.

Sensory Changes after Anterolateral Cordotomy

Careful determinations of changes in different mordalities of sensation were made on 20 individuals, five months to ten years after radical anterolateral cordotomy. 9 patients had complete relief of their former pain, 6 minimal discomfort which required no medication, and 2 moderate pain which could be controlled by small amounts of medication; 3 were classified as failures. Their sensory changes are listed in Table IV.

Table IV.—Analysis of Persistent Sensory Changes after Unilateral Anterolateral Cordotomy in 20 Patients

(6 *Cases at 5 Months to 2 Years; 14 Cases at 2 to 10 Years*)

Analgesia:	Complete to satisfactory level	13	
	Incomplete in parts of the formerly painful area	7	
Thermanæsthesia:	Hot and cold lost at same level	9	
	Hot lost 1–2 segments above cold ...	7	
	No complete loss to hot	3	No pain in 3
	No complete loss to hot or cold	1	

Relation of thermanæsthesia (to cold) to analgesia: Higher in 10; same in 6; lower in 4; 1 with sacral sparing to cold with analgesia complete in this area.

Touch acuity: Reduced 0 to sixfold. Maximum rise in threshold: Perception of 0·5 gramme von Frey hair on control side as compared with 3 grammes hair on analgesic side. Several others after operation were able to detect touch of a 0·25 gramme hair as well on the analgesic as on the control side.

Pressure pain on bone: Always reduced. Minimal rise in threshold from 26 lb. per sq. in. to 31 lb.; maximal rise from 10 lb. to unawareness of pressure of 52 lb.

Position sense: Unchanged.

Graphæsthesia: Reduced in 1 case only.

Two-point discrimination: Sharp point: Greatly reduced. Dull point: Only slightly reduced.

Localization of touch: Normal in all but 2.

Vibratory sense: Only minimally changed.

Thirteen of the 20 had analgesia with complete unawareness of sharp or disagreeable quality from the prick of a sharp pin. In 7 analgesia was incomplete in parts of the painful area. In 3 of these the operation had failed to relieve severe pain. Not only in these 20 patients, but also in the entire group, an analgesic level to within one segment of the tractotomy incision was rarely attained. This differs from Foerster and Gagel (1932), who described this result after operation in 16 patients, but conforms with most other observers.

Although in most of our patients no effort was made to raise the level of analgesia to its maximum height, our incisions in the cord were both deep and carried far ventromedially (fig. 1). The results indicate that the level of the incision should be at least four segments above the highest point at which the pain is felt. Even this interval will not always suffice. As an example we cite a patient previously cordotomized on four occasions, twice on each side, by a distinguished neurosurgeon elsewhere.

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Although we found bilateral hypalgesia to T5, the only true analgesia was confined to the sacral segments of one side. In our subsequent unilateral cordotomy at the second thoracic segment the highest level obtainable after four incisions to increasing depth was at the inguinal fold. Fortunately complete analgesia has persisted and he has continued to be relieved of his pain from lumbar arachnoiditis, not only in the analgesic zone, but in the contralateral hypalgesic limb as well.

Thermanæsthesia was more constantly complete than analgesia, as some residual awareness of heat was present only in 3; partial sensation to both heat and cold was retained in but a single instance. Despite some residual awareness of temperature, 3 out of these 4 had complete freedom from pain. Insensibility to cold extended above the level of analgesia in 10, was the same in 6, and a segment or two lower in 4.

The normal person feels the contact of a ¼ to ½ gramme von Frey hair as a sense of light touch over hairless areas. On the analgesic side the threshold to touch was unaltered in some, slightly increased in the majority, and to a maximum of sixfold in one. All were able to feel the touch of a 3-gramme hair. Tactile sensibility remains remarkably acute in hairy areas, so that the least contact is felt. We tell these patients that they will still be able to detect a mosquito when it alights although they will not be able to feel it bite or be annoyed by the subsequent itch.

Perception of pressure pain over bone is always reduced. In some individuals a maximum stimulus of 50 pounds per square inch did not hurt on the analgesic side, while 10 pounds was painful at standard control points. In others, the threshold for pain amounted to as little as 31 pounds on the analgesic side compared to 26 on the control.

Vibratory acuity was never more than minimally reduced. Localization of touch remained normal in all but 2 cases. Graphæsthesia was reduced in only a single instance.

Two-point discrimination was adequately tested in 14 patients using the two sharp points of a compass. In 3 of these two-point discrimination was likewise tested using two blunt points. For the latter tests the points of the compass were covered with corks, applied so that an area 1–2 mm. square was laid lightly against the skin. The separation of the compass points necessary to identify the two points was compared at corresponding locations on the normal and analgesic sides. Two-point discrimination using sharp points was moderately to markedly reduced in 12 of the 14 patients, i.e. the separation of the compass points necessary for discrimination was 2 to 5 times greater than that required on the normal side. In the remaining 2 patients there was only slight reduction of two-point discrimination using two sharp points. Of the 3 patients who were tested using blunt points, 2 showed only slight reduction and the other no

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reduction on the analgesic side. This may be related to the fact that a larger area of skin was stimulated by the corks than by the points. The location of the testing had no influence on the result, that is, there was equal reduction of two-point discrimination wherever the test was applied below the level of analgesia.

Position sense remained unchanged. The sense of tickle on the sole of the foot usually persists, although its intensity is often reduced. Itch from a poison ivy dermatitis was abolished in the analgesic zone in one patient tested, confirming Rothman's (1943) claim that itch is a form of pain sensation. Hyndman and Wolkin (1943) have tested 10 patients with itch powder (from *Mucuna pruriens,* obtained in novelty stores) and found that itching was abolished in the analgesic area. One patient has been observed outside this series in whom an agonizing itching associated with an intramedullary neoplasm of the cord was abolished following anterolateral cordotomy. Banzet (1927) has reported a case of severe itching with kraurosis vulvæ completely relieved by anterolateral cordotomy; relief was maintained when the patient was last seen two and a half years after operation.

In general, after the most radical transection of the anterolateral quadrant almost no useful sensation is lost except discrimination of temperature. There is no subjective numbness or unawareness of the analgesic extremity, nor any difficulty in identifying small objects, selecting materials, or performing the finest movements with the eyes closed. The patient walking barefoot in the dark can tell whether he is walking on a stone or wooden floor, on a carpet or on linoleum. He must only beware that he does not step on a tack or burn his foot on a hot object. There is no tendency in our cases to trophic changes, and injuries heal in normal fashion.

Certain other stimuli, however, are often capable of causing pain in "analgesic" zones (Table V). Stimulation with bipolar electrodes 2 to 3 mm. apart on the skin with 60-cycle current at from 40 to 140 volts is invariably disagreeable. This must be conducted over other pathways than the contralateral anterolateral column. The disagreeable quality of testicular compression is diminished but rarely absent on the analgesic side after unilateral cordotomy (*see* Table V). We had no male patients to test after medullary or high cervical tractotomies. The fact that two patients were able to feel unpleasant sensations following ankle fracture and thigh contusion came as a distinct surprise. These observations doubtless explain a certain number of failures to relieve suffering, as certain obscure disease processes may hurt in other ways than by the normal mechanism of pain ascending in the anterolateral tracts. Whether sufficient sensation is still preserved to serve as a warning in appendicitis,

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TABLE V.—TYPES OF STIMULUS OFTEN CAUSING PAIN IN "ANALGESIC" ZONES

	Pain on stimulus absent	*Pain on stimulus reduced as compared with normal side*
Achilles tendon pressure	6	6
Testicular compression	2	8
Pressure on bone (50 lb./sq. in.) ...	9	7
Hair pulling	17	3
Multiple rapid pin-pricks	8	12*
Bipolar electrical cutaneous stimulation (40–140 volts)	–	20
Trauma: Fractured ankle ...	–	1
Contusions to thigh ...	–	1

* Two patients had recurrence of severe pain with appearance of small scattered areas of disagreeable sensation to the "repetitive pin-prick test." Both of these have again been relieved by a secondary deeper cordotomy.

inflammation of the gall-bladder, or passage of a urinary calculus is still uncertain. However, we have seen no instances where such critical diagnoses have been missed on this score, and in patients with advanced malignant disease and its attendant complications accidents of this sort certainly have been reported. One of our patients who stepped on a nail found that he was adequately warned by the reflex withdrawal of his analgesic foot.

As pointed out above, the observations of cutaneous areas where single or rapidly repeated pricks with a pin may be felt as unpleasant but not sharp are of special importance. We believe that this indicates, in at least some patients, the presence of a few residual fibres transmitting pain in the contralateral anterior quadrant. 4 patients with recurrence of severe pain who would have passed as having a satisfactory level of total analgesia by the ordinary methods of testing have been relieved by secondary deeper incisions of the anterolateral quadrant.

VISCERAL SENSATION

Ranson (1947) in his textbook made the statement that, when "the spinothalamic tract" is cut on one side only, the analgesia of the opposite side of the body "involves the skin, muscles, fasciæ, tendons and bones, but not the viscera. Bilateral section is required to abolish visceral pain." The failure of hemisection of the cord to relieve biliary pain in dogs has been emphasized by Davis, Hart and Crain (1929). Hyndman and Wolkin (1943), who have reported testing an individual after unilateral anterolateral tractotomy, found that pain from distension of the renal pelvis was slight, but not abolished. It does not seem fair to conclude from a single experience after unilateral cordotomy that the renal pelvis has "a partial bilateral representation."

TABLE VI.—VISCERAL SENSATION AFTER UNILATERAL CORDOTOMY

Distension renal pelvis:	No pain	5
	Reduced pain	2*
Distension gut (Analgesic side):	No pain referred to analgesic side	7
	Reduced pain referred to normal side ...	5

* On control side 30 per cent less fluid induced pain and nausea.

The data recorded in Table VI tend to disprove the hypothesis that one-sided pain from a viscus travels upwards to a clinically significant extent in both anterolateral columns. 7 patients with satisfactory unilateral analgesia were tested by retrograde ureteral catheterization and distension of the renal pelvis. Injection on the control side of 8 or more c.c. of fluid invariably produced pain, and usually nausea, while a volume of 15 c.c. was easily tolerated on the side of the analgesia. In 5 volunteer subjects no sensation of pain was noticed, while in 2 others mild discomfort without nausea was experienced after injection of 30 per cent more fluid than could be tolerated on the normal side. Distension of intestinal loops at different levels on the analgesic side with balloons inserted under fluoroscopic control produced no discomfort in 7, while 5 others reported that milder pain was referred across the mid-line to the normal side. Further observations are necessary on this score and will be reported at a later date. We have also had a patient under observation in whom persistent pain after multiple operations on the biliary tract and pancreas. This operation was performed eight years ago, before we appreciated the effectiveness of sympathectomy in the relief of pain of purely visceral origin.

CAUSES OF FAILURE

As shown in Table II, C, 75 per cent of our patients maintained total or nearly total freedom from pain following interruption of the pain tract in the anterolateral column for periods from five months to ten years, and an additional 10 per cent maintained sufficient relief to eliminate the need for narcotics. The early and late failures deserve special consideration.

In the first place, it is of interest to study the conditions which failed to respond following an adequate level and degree of analgesia. These are listed in Table VII. The psychoneurotic constitution of the first patient made any evaluation of her complaints impossible. The second and third patients, with painful leg and arm phantoms, continued to complain of their original symptoms, despite analgesic levels which were complete to T5 and C3. It is, of course, impossible to determine by objective testing the interruption of all pain fibres from an amputated part. We are in disagreement with the opinion of Bailey and Moersch

(1941) and many others that radical transection of the anterolateral column usually fails to relieve painful phantom sensation. Six other sufferers from this condition in the lower extremity have been relieved over periods from five months to two and a half years. Two others afflicted with painful phantom arms were relieved of their pain as long as analgesia above C5 was complete, but had recurrences at three months and three years when analgesia was replaced by hypalgesia. The potential effectiveness of high cervical cordotomy in the relief of arm phantoms has been substantiated by Falconer and Lindsay (1946). The failure to relieve the pain of arachnoidal adhesions in Cases 6 and 7 is perhaps explainable on the basis of coexistent intrinsic disease of the spinal cord proper (*see below*). Satisfactory results were obtained in 6 other patients with similar levels of analgesia.

As for the failures with Mary Y. and Frank T., we now doubt that painful muscular spasms, which often accompany disease of the spinal cord can be relieved by anterolateral cordotomy. In our opinion this is often also true of the pain occurring as a sequel to complete or partial transection of the cord, as exemplified by Jeremiah O. and Arthur T. While this is also the opinion of Davis and Martin (1947) from their extensive study of recent war injuries, pain in 5 patients following lesions of the spinal cord proper has been relieved according to the earlier reports of Frazier (1920) (Case 2), Frazier and Spiller (1923) (Case 8), Leighton (1921) (Case 2), Banzet (loc. cit.) (Case 27), and Foerster and Gagel (loc. cit.) (Case 28). There is no question about the effectiveness of the operation after injuries of the cauda equina, where we have had complete relief in each of 4 patients with satisfactory high levels of analgesia. Equally encouraging results have been reported by Freeman and Heimburger (1947), Botterell *et al.* (1946), and Kahn and Peet (loc. cit.).

With the exception of pain resulting from injury or disease of the spinal cord proper, there are few varieties of persistent organic pain in the lower part of the body which cannot be relieved by a well-performed cordotomy. As seen in Table VII, such failures occurred only in the first case, a psychoneurotic woman with post-operative pain, in a single case of painful phantom leg, and in the two others with arachnoiditis. In the latter there may have been coexistent involvement of the cord as well. In the large group of patients suffering pain from advanced malignant disease there was but a single failure to control pain of the contralateral side when the level was adequate and analgesia complete. Case 8 in this situation again developed pain in his analgesic leg when his sarcoma spread to involve the twelfth thoracic vertebra and ribs.

In an attempt to develop a satisfactory method of eliminating failures where the focus of pain is central (i.e. within the spinal cord, thalamus,

TABLE VII.—RETURN OF PAIN DESPITE ANALGESIA—10 CASES

	Patient	*Type of lesion*
1	Jennie S. MGH U No. 1898	Persistent abdominal pain following nephropexy. Severe psychoneurosis.
2	Frank I.* MGH U No. 552763	Amputation stump neuralgia and phantom leg, following hip disarticulation with recurrent chondrosarcoma of acetabulum. No additional relief was obtained by section of ipsilateral posterior column of Goll, but patient was greatly improved by frontal leucotomy.
3	Robert S.* MGH U No. 573480	Post-amputation phantom hand following crush in machine. Pain continued despite satisfactory level to C3.
4	Mary Y. MGH U No. 606632	Paget's disease, fracture T11 vertebra, and degenerative arthritis of hip. Painful flexor spasms in legs and cord lesion.
5	Frank T. MGH U No. 205110	Diabetes and combined system disease. Painful flexor spasms in legs and cord lesion.
6	George P. MGH U No. 180510	Left-sided sacral neuralgia of unknown origin which had been treated by intrathecal injection of alcohol at another hospital. Severe sacral arachnoiditis discovered at exploratory laminectomy. Failure of cordotomy despite analgesia to T8.
7	Hamilton I. MGH U No. 19391	Arachnoiditis with residual burning pain in foot. Relieved subsequently by unilateral frontal leucotomy (Dr. J. E. Scarff).
8	Arthur R. MGH U No. 270774	Osteogenic sarcoma of sacrum. Pain in leg relieved, but returned when osteogenic sarcoma spread to T12 vertebra and ribs despite continued analgesia of lower extremity.
9	Jeremiah O.* MGH U No. 521939	Pain from complete crush of mid-thoracic cord not relieved by subsequent resection of scarred rostral end of severed cord.
10	Arthur T.* MGH U No. 569083	Old tuberculosis of spine with kyphosis and cord compression at T7.

* In these patients it was impossible to test for residual islands of perception of repetitive pin-prick.

or cortex), rather than peripheral, we have tried preliminary subarachnoid spinal block with procaine. This interrupts conduction in the spinal and caudal sensory roots, but does not penetrate deeply into the cord. First attempts with differential blocking of the finer calibre, less heavily myelinated pain fibres in the spinal roots by low concentrations of procaine, as suggested by Sarnoff and Arrowood (1946), were most misleading. In some cases, which later responded well to cordotomy, the pain was actually increased. When 150 mg. of procaine dissolved in 4 c.c. of spinal fluid were injected the temporary effect corresponded fairly well with the final outcome of tractotomy. Geoffrey Jefferson (1950), who has been employing this test since 1924, states that he has been impressed by its effectiveness. In our experience with 10 cases, a favourable result was correctly predicted in 8 and a poor result foretold in 1 (the psychoneurotic

Case 1 of Table VII). On the other hand, there was an erroneous prediction of failure in a patient who had no relief from two spinal anæsthetics in which loss of sensation extended to T11 and T4 respectively. This man's thigh amputation stump and phantom pain, nevertheless, responded well to operation. Further experience with the test is therefore essential, and it must be borne in mind that injections of large concentrations of procaine may be dangerous in persons with arachnoiditis or other forms of intraspinal disease. At present, therefore, we have no certain method of picking in advance the rare individual who will fail to derive a satisfactory result following a technically adequate cordotomy.

In order to ensure the success of the procedure it is our opinion that the most important step is to establish the level of analgesia at the time of operation. The initial incision is rarely deep enough. A second or even a third is usually necessary, and at times all of us have been forced to make additional incisions of progressively greater extent. It is therefore vital that every attempt be made to perform this operation under local anæsthesia, or under local, supplemented by pentothal and nitrous oxide, and the patient given time to awaken. When this is done, a certain number will be too unco-operative or confused for satisfactory testing on the table. The depth and extent of incision must then be a matter of judgment. If the result is unsuccessful, the incision should be reopened on the following day in order to deepen the cordotomy and extend it further forward towards the mid-line.

In the earlier years of this series our efforts to establish an accurate sensory level at the time of operation were not as painstaking as at present. Nevertheless, it has been possible to carry out the test on nearly two-thirds of the total series. Neglect to do so has doubled the risk of early failure in our hands. Unfortunately, this precaution does not eliminate later failure caused by a drop in the level of analgesia, as there is no way of distinguishing between the immediate analgesia due to "spinal shock" and actual transection of the pain fibres. If the level of analgesia is tested at frequent intervals during the first hours after cordotomy, it may be found to climb several segments. This is due to the spread of œdema beyond the plane of transected fibres. Analgesia will drop again to at least its original level. At times, however, analgesia will give way to hypalgesia only after a period of months. It is possible that in such instances there may be late recovery of the fibres contused but not transected at operation. We are still uncertain whether or not there may be recovery of pain sensation a year or more after cordotomy. When analgesia fades a variable degree of hypalgesia is left in its place, often insufficient to prevent complete return of pain. This late increase in pain conduction is the hazard which the skilful surgeon has most to fear. We

have now reoperated on a number of these later failures with gratifying success.

Discussion

Anterolateral cordotomy has been accused of yielding a high proportion of failures and uncertain results. In addition to the common failure to establish a satisfactory level of analgesia by testing at the time of operation under local anæsthesia, it is the practice of many surgeons to make the laminectomy too low in the back and not to carry the cordotomy incision close enough to the centre of the cord or far enough ventromedially. Inaccurate illustrations of the proportion of anterolateral quadrant occupied by the pain pathway in current medical textbooks explain the conservative nicks which are all too often made. The fibres conducting pain are not confined to a narrow compact band in each anterolateral column. Foerster and Gagel (loc. cit.) illustrate massive surgical lesions in post-mortem photomicrographs of patients who had undergone successful cordotomy which are very similar to our fig. 1. If Hyndman and Wolkin's (loc. cit.) figures are taken to represent the actual size of the spinal pain pathway, and its large extent kept in mind, the proportion of successful results will be materially increased. It is our impression that fibres run even deeper and in closer proximity to the ventral horn, at least in certain subjects. There is fortunately no evidence that widening the extent and increasing the depth of cordotomy appreciably raises the incidence or severity of post-operative complications.

Inadequate post-operative testing to determine the completeness of analgesia is another cause for unjust evaluation of the procedure. It is our contention that analgesia, to be effective, must be complete as well as adequate in extent. A single prick or the continuous scratch of a sharp pin must evoke no quality of disagreeable sensation, even over any small cutaneous islands. Furthermore, in the early post-operative period rapid repetitive pin-prick should produce no sense of sharpness or discomfort. Careful stimulation of the entire "analgesic" zone is essential. If any islands of dysæsthesia are present it is unfair to blame the operation for the continued presence of pain, because it will usually disappear after a more radical tractotomy.

The recent tendency to substitute bilateral frontal leucotomy for the relief of pain which can be controlled by cordotomy is deplorable. We have used this operation in numerous cases of carcinoma of the oropharynx and supraclavicular region, atypical neuralgia of the head, etc., and have followed them in the hospital and in their homes with members of the Psychiatric Service. All of them showed severe changes in personality and were quite incapable of leading an independent existence. This has even been true in a number of our 15 cases of unilateral frontal leucotomy

(Bonner, 1950) although not observed by Scarff (1949) in his recent series. For this reason we shall continue to recommend cordotomy whenever there is any reasonable chance of success, even if failures occur in a small proportion of patients with widespread malignant disease or refractive phantoms after amputation. Only in these is leucotomy justified.

Summary

(1) Results in 241 anterolateral cordotomies performed on 210 patients between 1936 and 1948 have been analysed statistically, and 20 available for late examination after an interval of five months to ten years submitted to careful neurological investigation.

(2) In the whole series, evaluated at the time of discharge from the hospital, failures amounted to 9 per cent; in the series followed from five months to ten years 15 per cent had pain which was still incapacitating. We have attempted to explain the reasons for these early and late failures. Early post-operative persistence of pain is due primarily to a lack of total analgesia to the necessary level or to poor selection of cases. Technical skill and experience should make it possible to minimize these defects. Late return of pain is caused by a drop in the sensory level, the development of hypalgesia, or by the extension of malignant disease—factors which the surgeon often cannot control. Operation under local anæsthesia, deep transection of the anterolateral column, and careful verification of the extent of sensory loss will greatly reduce the incidence of early failures.

(3) Aside from analgesia and thermanæsthesia, sensation is altered to only a minor degree.

(4) The degree of analgesia may not be clinically satisfactory if there is any disagreeable quality to the prick or scratch of a pin over even small islands of skin. In the early post-operative period rapid repetitive pin-pricks also should evoke no discomfort. Unless these criteria are met pain is likely to recur, but may again be abolished by more radical cordotomy.

(5) Analysis of the complications shows that urinary retention cleared within two weeks in all but 5 per cent after unilateral operation. After bilateral one-stage cordotomy 29 per cent of patients suffered some degree of urinary disability at the time of discharge from the hospital, but only half this number when the operation was performed in two stages. While we do not have satisfactory statistics on duration of this complication after bilateral tractotomy, none of the patients examined five months or more after unilateral section had any obvious disturbance in bladder control.

(6) Occasional weakness of the leg on the side of the cordotomy and

impairment of anal sphincter tone nearly always disappear within a year. Even the initial reduction of sexual gratification, observed in both sexes, is likely to improve with time.

(7) The mortality rate of the operation amounted to 4 per cent.

Conclusions

We believe that anterolateral cordotomy is the best operation for relief of most varieties of unilateral chronic pain situated below the first thoracic dermatome. When properly performed it is highly effective and carries a remarkably low risk of serious long-standing complications. We are not yet sure of its effectiveness when the brachial plexus is involved.

The bilateral operation involves a greater risk, but far less than the certain alteration in personality and impairment of higher intellectual processes that accompany bilateral frontal leucotomy. The latter is a justifiable substitute only when pain is present in the upper cervical dermatomes, or in both sides of the upper thorax.

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PLATE XV

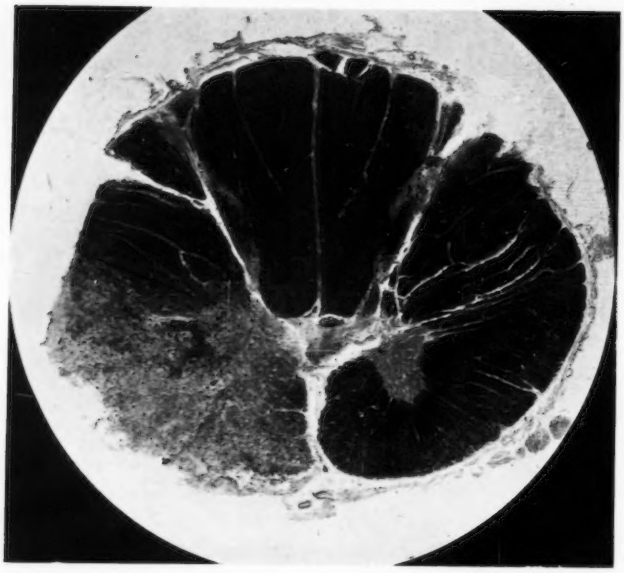

FIG. 1.

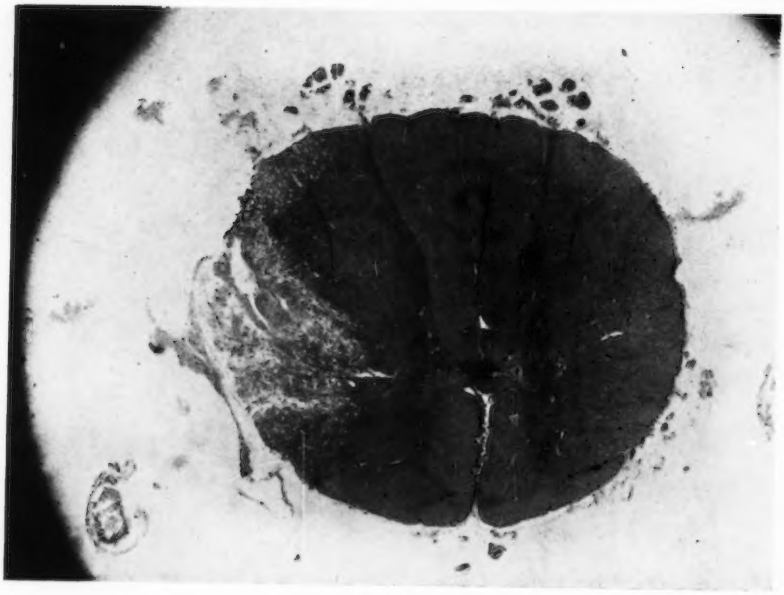

FIG. 2.

To illustrate article by James C. White, William H. Sweet, Ralph Hawkins and Richard G. Nilges.

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LEGENDS FOR PLATE XV

FIG. 1.—Cross section of spinal cord at T2. Left anterolateral cordotomy had been performed on this 65-year-old sea captain for low back and right pelvic pain from recurrent carcinoma of ascending colon. There was analgesia to umbilicus with hypalgesia to xyphoid. Relief of pain was complete and there was no complicating leg weakness. Cystometrogem on seventh day was normal and he began to urinate. Despite normal intravenous pyelogram before operation the patient developed uræmia from ureteral compression and died after eighteen days.

FIG. 2.—Cross section of spinal cord at level of lower incision (T3) eighteen days after bilateral anterolateral cordotomy. This woman with advanced carcinoma of cervix uteri was fully relieved of her low back pain with radiation to both legs. Level of analgesia was at T11 on right and T10 on left. She had no significant leg weakness and began to void normally on the eleventh post-operative day. Death was due to uræmia from ureteral compression.

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THE ORIGIN, COURSE AND TERMINATION OF THE PREFRONTO-PONTINE TRACT IN THE HUMAN BRAIN

BY

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In previous publications from this laboratory (Meyer, Beck and McLardy, 1947; Meyer, McLardy and Beck, 1948) evidence was presented, supporting the existence of prefronto-pontine tract—Arnold's bundle[1]—which was found to be degenerated in four out of five brains with various leucotomy lesions. From the case material available at that time, however, final conclusions regarding its origin, course and termination could not be drawn. In this study, therefore, the problem will be re-examined on a larger material, better suited to clarify these points and to throw some light on the cause of the many contradictory statements prevalent in the literature.

Material and Methods

From a material of 130 leucotomy brains collected in this laboratory, 5 cases with suitable anterior lesions were chosen, who died from intercurrent disease after a survival time ranging from one year eight months to three years ten months. Four of these cases showed lesions, which in both sides terminated macroscopically anterior to the genu corporis callosi, that is to say at a coronal level where almost the entire cortex belongs to the prefrontal granular type.[2] The fifth brain showed a similar lesion on the left side only, while on the right side a more posterior cut encroached upon fibres from dysgranular and agranular cortex, sparing those from anterior prefrontal regions. Owing to this asymmetry the case contributed largely towards the evaluation of different components of the prefronto-pontine tract. In all 5 cases the lesion consisted of a smooth-walled cyst with a very narrow zone of demyelination around it.

[1]The term "Arnold's bundle" seems to be differently interpreted by various authors; some imply by it a prefronto-pontine, others a fronto-pontine tract. In this study it will be used in the former sense, although, as will be seen later, fibres from dysgranular and agranular frontal areas also enter into its composition.

[2]For the purpose of this paper the term "prefrontal cortex" is meant to include only areas in which the internal granular layer is well developed and to exclude —contrary to customary usage—dysgranular transitional zones (i.e. area 8/FC and the transitional and agranular cortex on the orbital surface).

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A sixth case was that of a woman with a head injury of several years standing, whose brain showed circumscribed destruction of prefrontal areas, on the right side confined to the extreme pole.

For the study of individual variations some further 22 leucotomized brains were utilized, although their lesions, mostly situated in a more posterior plane, damaged fronto-pontine fibres in addition to Arnold's bundle. They will, therefore, be mentioned only collectively, with the exception of Case 7, which will be described in detail.

After fixation in 10 per cent formalin, blocks containing in unbroken continuity the cortical lesion, striatum, thalamus and brain-stem extending caudally to mid-pons and, in Cases 1 and 5, to mid-medullary level, were embedded in celloidin and cut serially at a thickness of 30μ. Every hundredth section from the cortical lesion, every fiftieth from the subcortical grey centres was stained by the Nissl method, a neighbouring section by the Heidenhain modification of Weigert's method. A few sections at appropriate levels were impregnated by the Glees silver method, to show unmyelinated fibres. The degenerated fibre tracts were traced by means of their apparent gliosis in Nissl preparations, a technique for which comparatively thick sections are imperative, since they show even moderately gliosed bundles very distinctly. The gliosis consisted in all instances of oligodendroglia cells, often arranged in long, dense chains; hardly any astrocytic nuclei were present.

In addition the remainder of the frontal cortex posterior to the lesion was investigated in serial sections, to exclude the possibility of a causative or even contributory factor from incidental lesions in dysgranular or agranular frontal cortex.

In those cases where the serial sections ended at mid-pons level sample sections from lower pons and medulla were investigated.

The primary lesions were studied microscopically to their full posterior extent and the numerals inserted in figs. 1, 3, 5, 6, 8, 10 and 12 correspond to the actual cytoarchitectonic structure as encountered in each section[1] To check areal involvement still further (especially the damage done to fibres *en route* from undestroyed cortex), retrograde sector-degeneration in the various thalamic nuclei was utilized, and served in each case to supplement the final assessment of the extent of the primary lesion. All this, together with a careful microscopical search for incidental lesions

[1] The terminology used in this study is that of both Brodmann and Economo and Koskinas (the latter's being omitted from the diagrams): homology is based on Rose's (1935), Bailey's (1948) and our own observations. For the orbital surface my previously suggested terminology (1949) has been adopted, since neither Brodmann's nor Economo and Koskinas' did full justice to its more complex structure.

in the frontal lobes posterior to the leucotomy cut, should ensure an accurate estimate of the areas responsible for any secondary degeneration.

Figs. 1–12 represent projection drawings of the surface outlines of frontal cortex, thalamic nuclei and brain-stem respectively, done individually for each hemisphere. This was found to be a more satisfactory method than using the same standardized diagram throughout, as it does more justice to the absolute and relative size of the lesions. Cross hatching in these diagrams indicates the severest lesion, single hatching and broken lines a gradual decrease in severity; degenerated fibre tracts have been represented by stippling and/or solid black areas. Fig. 13 does not refer to any specific case, but is meant to illustrate the position of the prefronto-pontine tract at all representative levels. Here the course taken by the fibres is indicated by black areas throughout, which would include in the anterior limb of the internal capsule the anterior thalamic radiation as well as the prefronto-pontine tract, since both run together and cannot be distinguished in Nissl preparations. Only from the level of the genu capsulæ internæ onwards is it possible to separate the two bundles (cf. Meyer, Beck and McLardy, 1947, fig. 19).

Throughout, left and right sides have been drawn as if observed from the posterior surface.

Observations

Case 1.—F. M. was a woman who died from carcinoma of the cervix, aged 69, two years two months after prefrontal leucotomy.

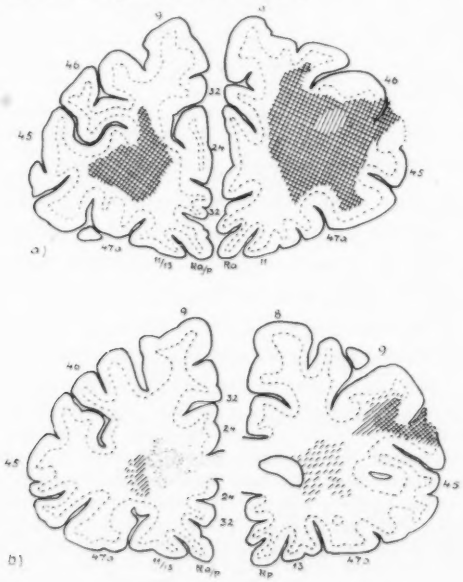

Fig. 1.—*Case* 1.

Left Hemisphere.

Cortical lesion (fig. 1a, b).—A smooth-walled cyst, greatest in extent at the level of the most anterior tip of the gyrus cinguli, occupies the centrum semiovale. It involves fibres from areas 46/FD$_{\Delta}$, 45/FD τ, 47 anterior, 24/LA and the most antero-dorsal portion of area 9/FDm. All connexions with the extreme pole-area 10/FE- are severed and from retrogade degeneration in the dorsomedial nucleus (fig. 2) it can be deduced further, that fibres to the medial orbital cortex—areas recta anterior and 11—must have been involved. The lesion terminates posteriorly in the deep white matter of the hemisphere at the level of the most anterior tip of the genu corporis callosi. Figs. 1 and 2.

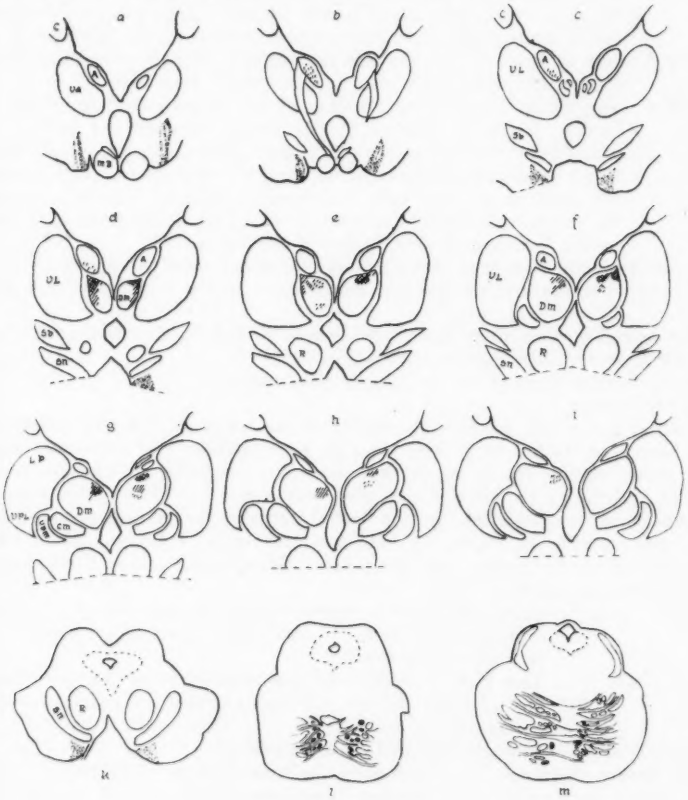

FIG. 2.—*Case* 1.

In this and subsequent diagrams of the secondary lesions the degenerated fascicles in the pons have been indicated by black areas. The reticular and intralaminar nuclei of the thalamus have been omitted, since they bear no relation to the problem.

Secondary degeneration (figs. 2, 13).—Distinctly gliosed fascicles can be traced through the following levels (these levels, illustrated in fig. 13, are intended to form the basis for the description of the secondary degeneration in all the subsequent cases, in which they will only be referred to by their respective numbers):

Level 1: The most anterior portion of the internal capsule, where they occupy the entire dorso-ventral extent of its bundles.

Level 2: The internal capsule at the tip of the anterior perforated space, where they shift medially in the dorsal half of its bundles, but still fill the entire ventral bundles.

Level 3: The internal capsule at the beginning of the globus pallidus, where the gliosed fascicles converge, to occupy only the ventral-most portion, remaining in this position to

Level 4: The beginning of the thalamus. Here the gliosed bundle divides into a medial portion, which swings towards the thalamus (i.e. anterior thalamic radiation), and a lateral portion, which for a short distance lies laterally adjacent to the reticular nucleus of the thalamus to pass

Level 5: Just in front of the subthalamic nucleus, through the diffuse portion of the substantia nigra—whose cells remain intact—into

Level 6: The cerebral peduncle, running within its medial sixth (Plate XVI, fig. 3). It can be followed in this position through the peduncle into

Level 7: The medial bundles of the pons, thus splitting up into small fascicles which gradually disappear at the level of the decussation of the trochlear nerve in an essentially ventromedial position. The cells surrounding the gliosed fascicles appear shrunken, darkly stained with pyknotic nuclei, but there is no evidence of cellular outfall.

Apart from those degenerated fascicles which are seen passing at level 5 no gliosis can be traced into the stratum intermedium or the substantia nigra at any point.

The caudal portion of the brain-stem to mid-medulla level including the bulbar reticular formation does not show any gliosis.

Demyelination throughout the course is very slight.

Right Hemisphere.

Cortical lesion (fig. 1a, b).—The extent of the lesion on this side differs somewhat from that on the left. It is situated more laterally and terminates slightly more posteriorly at the tip of the anterior horn, involving in addition to areas 46/FDΔ, 45/FDτ, 47 anterior and most antero-dorsal 9/FDm, a more substantial portion of area 9/FDm on the lateral surface; the medial orbital surface, areas recta anterior and 11, on the other hand, and area 24/LA are spared. Retrograde thalamic degeneration does not point to involvement of any further regions.

Secondary degeneration (figs. 2, 13).—

Levels 1 and 2: Gliosed fascicles occupy the entire dorsal half of the internal capsule, while in the ventral half a certain proportion of its bundles appear normal.

Levels 3–7: The gliosed bundle appears slightly more compact than on the left side, but is otherwise identical in course and distribution.

Demyelination, although still mild, is more evident.

No further significant lesion is seen in the frontal lobes. Representative blocks from various parts of the brain appear intact, apart from a small vascular lesion in the left angular gyrus.

Case 2.—L. P. was a woman, who died from pulmonary tuberculosis, aged 47, three years 10 months after prefrontal leucotomy.

Left Hemisphere.

Cortical lesion (fig. 3a–c).—The lesion, a smooth-walled cyst, is situated in the deep white matter of the hemisphere, of greatest extent at the level of the precallosal portion of the gyrus cinguli and terminating posteriorly at the most anterior tip of the genu corporis callosi. In this position it involves fibres from areas 46/FDΔ, the most anterior portion of 45/FDτ, and 9/FDm, as well as areas 24/LA and 32/FDL. In addition the major part of the projections from the frontal pole area 10/FE is likely to be interrupted and retrograde degeneration in the

dorsomedial nucleus suggests a slight infringement on fibres to area 47 anterior. The medial orbital region is intact. Figs. 3 and 4.

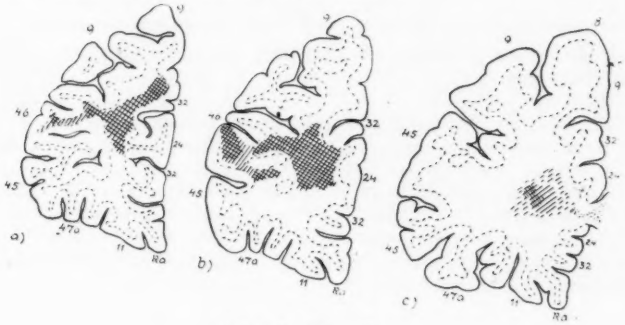

FIG. 3.—*Case* 2.

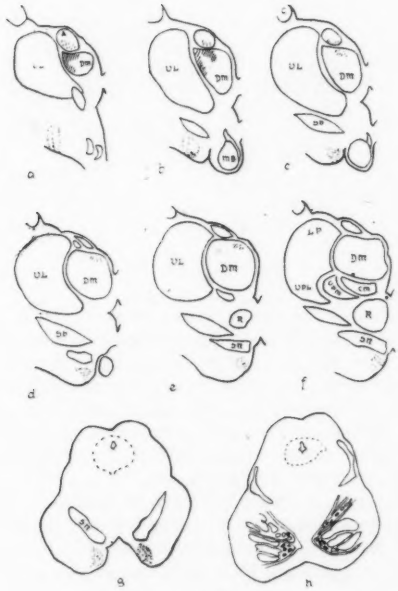

FIG. 4.—*Case* 2.

Secondary degeneration (figs. 4, 13).—Mildly gliosed fibre tracts can be followed through the internal capsule and peduncle into the antero-medial bundles of the pons. Their position is almost identical to that in Case 1 Right; the density of their gliosis throughout, however, is of a milder degree. This is especially noticeable in anterior levels, where the gliosis only fills the centre of the bundles in the internal capsule, leaving the periphery intact. Demyelination throughout is very slight.

No degeneration is to be found in lower levels of the pons or in the bulbar reticular formation.

The frontal lobe posterior to the lesion appears normal.

The *Right Hemisphere* shows an almost identical cortical lesion and secondary gliosis.

Representative blocks from other parts of the brain appear normal.

Case 3.—M. U. was a woman, who died from phthisis, aged 42, three years after prefrontal leucotomy.

Left Hemisphere.

Cortical lesion (fig. 5a, b).—At the level of the precallosal portion of the gyrus cinguli, a large cystic cavity replaces almost the entire white matter of the hemisphere. Anteriorly it completely isolates the frontal pole, posteriorly it rapidly diminishes and terminates still in front of the genu corporis callosi. Fibres from areas 10/FE, 46/FD Δ, 24/LA and 32/FDL are heavily involved and in addition those from the most anterior parts of areas 9/FDm, 45/FD τ and 47 anterior. The medial orbital region is spared. Retrograde changes in the dorsomedial nucleus do not indicate any additional damage. Fig. 5.

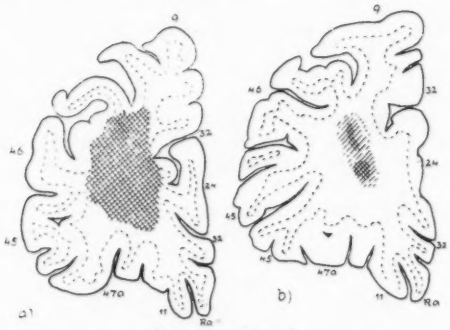

FIG. 5.—*Case* 3.

Secondary degeneration.—The resulting gliosis is in course and severity identical to that of Case 2 Left, demyelination being equally slight. No additional lesion is seen in the frontal lobe posterior to the leucotomy cut.

The *Right Hemisphere* shows a slit-like lesion, situated dorsolaterally and terminating in a more posterior plane than that on the left side, i.e. at the beginning of the anterior horn. The lesion involves fibres from areas 46/FD Δ, 45/FD τ, and 9/FDm and gives rise to a distinct gliosis within the medial-most portion of the cerebral peduncle, traceable into the pons.

Since, however, this side of the brain is very distorted and furthermore the medial half of the dorsomedial nucleus badly damaged at post mortem, a more detailed evaluation of the results will not be attempted.

Case 4.—J. A. was a man, who died from phthisis, aged 34, two years after prefrontal leucotomy.

Left Hemisphere.

Cortical lesion (fig. 6a–c).—The left hemisphere contains two large, but shallow, smooth-walled lesions, divided by a narrow bridge of tissue, which are maximal in extent at the level of the precallosal portion of the gyrus cinguli. Here they replace almost completely the white matter of the hemisphere, but diminish rapidly in size and terminate anteriorly in an exclusively dorsal position, and posteriorly—at the level of the genu corporis callosi—in a slightly more lateral position. The lesions involve, with the exception of area recta anterior and parts of area 11, fibres from the entire cortical circumference, including the dysgranular area 8/FC and they interrupt all connexions with the frontal pole. The dorsomedial nucleus shows degeneration in the corresponding sectors. Figs. 6 and 7.

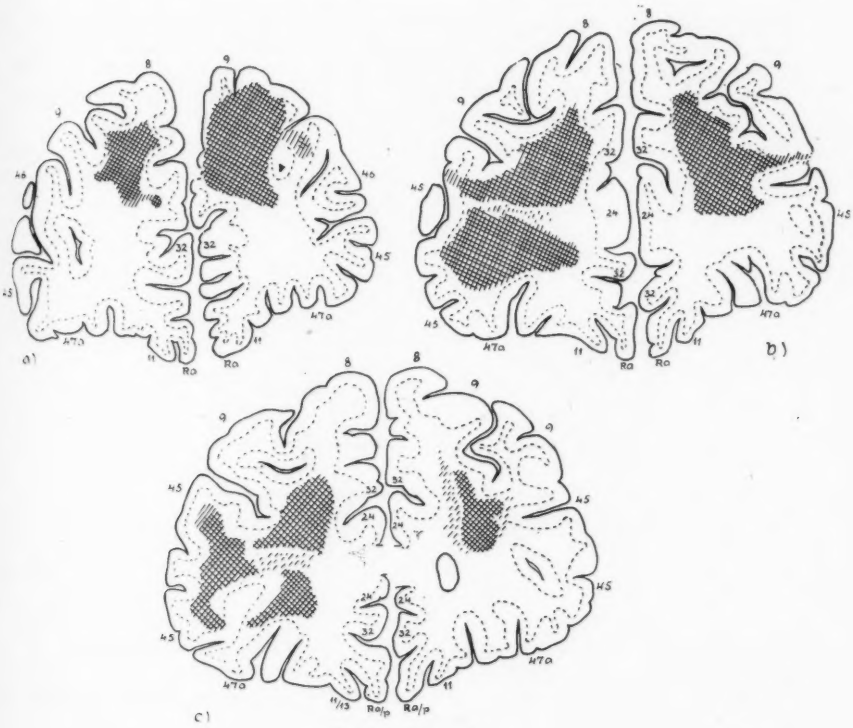

FIG. 6.—*Case* 4.

Secondary degeneration (figs. 7, 13).—Markedly gliosed bundles stand out very clearly throughout the different levels. Within the internal capsule their position is similar to that in Case 1 Right, a proportion of the ventral bundles in Levels 1 and 2 appearing intact, probably due to the escape of the medial orbital region. The ventralward shift of the bundles, however, is only completed in a slightly more posterior plane, in accordance with the more posterior level of the cortical lesion. On entering the cerebral peduncle (Level 6) the gliosis appears to be very compact and to occupy a larger area in medio-lateral extent than in any of the previously described cases. In conformity with these cases, however, it is situated in the immediate proximity of stratum intermedium and substantia nigra, without projecting into either at any point. There is a distinct demyelination within the corresponding part of the peduncle. The degenerated tract can be followed into the medial bundles of the pons, where it is surrounded by shrunken, darkly stained nerve cells. No gliosis can be traced into lower levels of the pons or into the bulbar reticular formation.

Right Hemisphere.

Cortical lesion (fig. 6a–c).—The leucotomy lesion on this side approximately corresponds in extent to the dorsal cyst in the left hemisphere. The only difference is, that anteriorly the cortex of the dorsal convexity is more directly damaged. Area 9/FDm is heavily involved, fibres from areas 46/FDΔ and 45/FDτ and the cingular cortex to a lesser degree; and although a participation of fibres from area 8/FC might seem likely from fig. 6b, this is not confirmed by retrograde degeneration

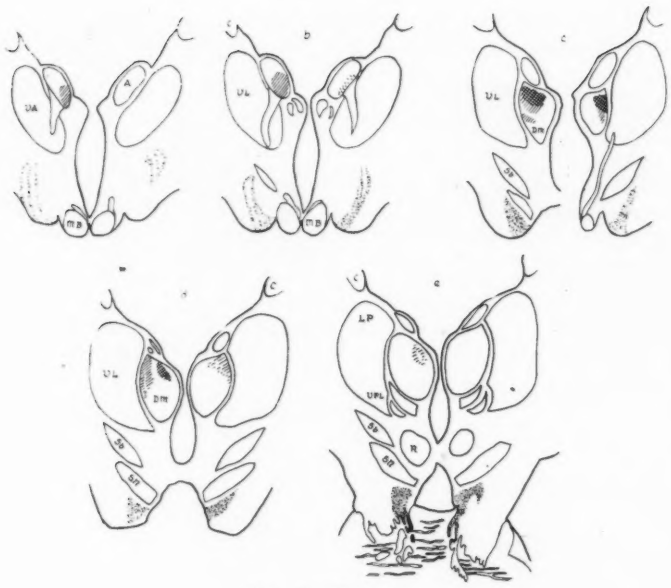

FIG. 7.—*Case* 4.

in the thalamus. The orbital cortex including area 47 anterior is preserved. A proportion of fibres connecting area 10/FE might be severed.

Secondary degeneration (figs. 7, 13).—The right hemisphere likewise displays distinctly gliosed fascicles at all levels. The gliosis, however, is slightly less compact than on the left side and, owing to the complete escape of the orbital region, situated (at Levels 1 and 2) exclusively in the dorsal half of the internal capsule. Within the affected bundles a narrow lateral strip is spared. In the caudal course the distribution of the degenerated fascicles is identical to that on the left side, except for the size of the gliosed area within the peduncle, which is slightly smaller (cf. fig. 7c Left with 7d Right). Demyelination throughout the course is very slight. The pontine cells surrounding the medial gliosed bundles are shrunken. Lower levels of the pons and the reticular substance of the medulla are intact.

Both frontal lobes posterior to the lesion, as well as sections from various parts of the brain, appear normal.

Case 5.—A. B. was a man, aged 65, who committed suicide by carbon monoxide poisoning one year eight months after prefrontal leucotomy.

This case has been included in virtue of its very asymmetrical lesion. It is in fact the only case among those six presented in detail, with encroachment on fibres from agranular area 6/FB. While thus on the right side a rather posterior lesion involves this area, but spares prefrontal projections, a more anterior lesion on the left side is exclusively confined to granular prefrontal regions.

Left Hemisphere.

Cortical lesion (fig. 8a, b).—In the left hemisphere at the level of the precallosal portion of the gyrus cinguli, a smooth-walled lesion occupies the ventromedial segment of the centrum semiovale; it terminates a short distance posteriorly, at the tip of the anterior horn within the pathway of the projections from more anterior prefrontal areas. The lesion affects fibres from areas recta

anterior, 11, 47 anterior 32/FHL and 24/LA and interferes in addition—according to retrograde degeneration in the dorsomedial nucleus—with the connexions of areas 9/FDm, 46/FDΔ, 45/FDτ and most probably 10/FE. The dysgranular area 8/FC is unimpaired. Figs. 8 and 9.

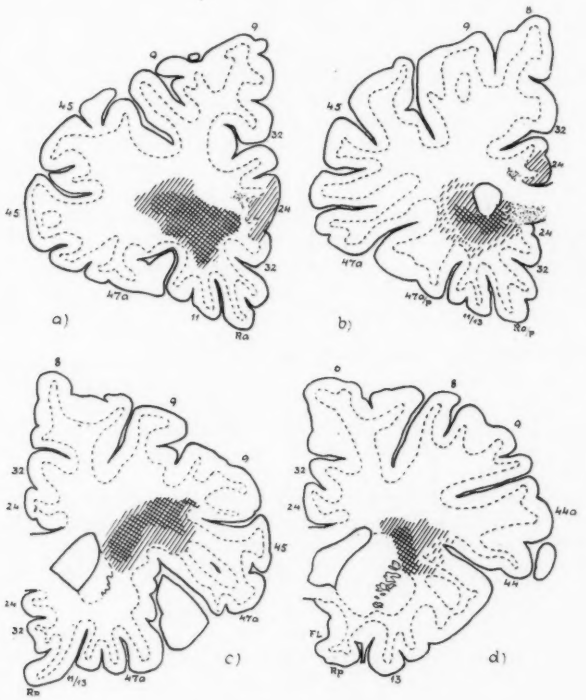

FIG. 8.—*Case* 5.

Secondary degeneration (figs. 9, 13).—The position of the degenerated fascicles in the internal capsule (Levels 1–4) is almost identical to that outlined for Case 1 Left. In the cerebral peduncle the bundle completely fills the medial sixth and within this area appears very heavily gliosed and markedly demyelinized (Plate XIX, fig. 3). In fact secondary degeneration in this case is the severest encountered in the whole of the material. At pontine level (7) the gliosis splits up to occupy the small medial-most fascicles (Plate XVI, fig. 4), shifting further caudally to an entirely ventro-medial position. The degeneration gradually begins to disappear at the level of the caudal extremity of the trigeminal motor nucleus; the number of shrunken nerve cells around the gliosed bundles (Plate XVII, fig. 2) diminishing in proportion. At the level of the abducens nucleus gliosed fascicles are no longer apparent, and the remainder of the brain-stem down to the medulla appears perfectly normal.

Right Hemisphere.

Cortical lesion (fig. 8c, d).—A smooth-walled cyst, its long axis orientated latero-medially, occupies the deep white matter of the hemisphere at the level of the head of the caudate nucleus, without, however, involving the latter or rupturing the wall of the lateral ventricle. It terminates about 7 mm. posteriorly in a

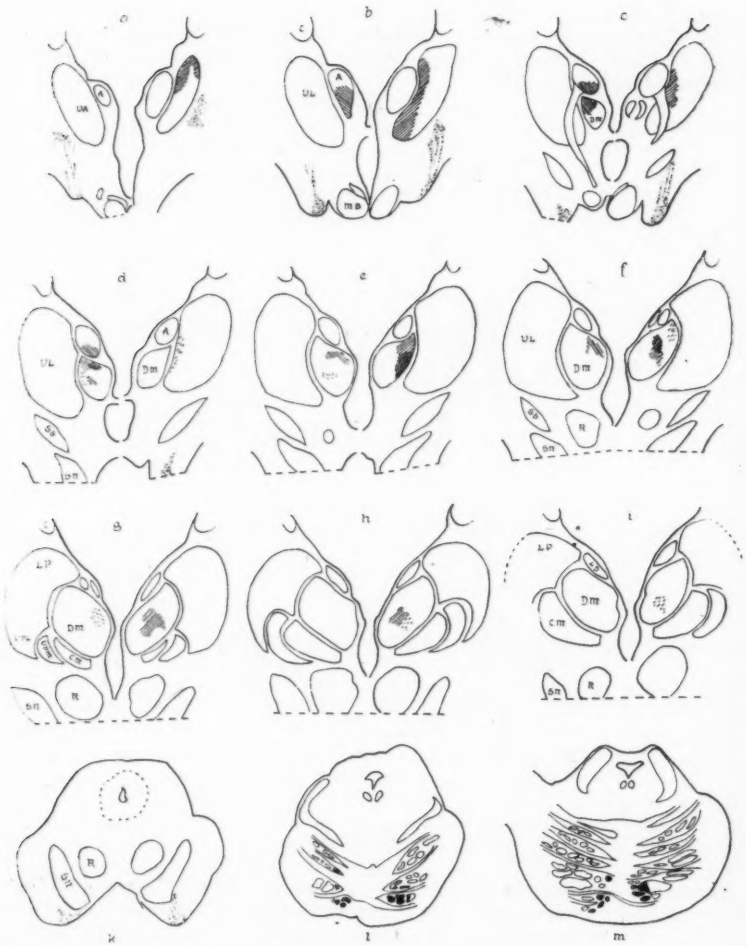

FIG. 9.—*Case* 5.

similar position and in immediate proximity to and slightly impairing the most dorsal margin of the caudate nucleus, but sparing the internal capsule as well as the putamen. The lesion affects fibres from postero-lateral area 9/FDm and the most posterior part of area 45/FD Δ, but does not interfere with any projections to and from more anterior prefrontal cortex, since the internal capsule, which carries these fibres, remains intact (cf. fig. 9d, e). From retrograde degeneration in the thalamus it is apparent that some fibres to area 6/FB (fig. 9a–d) and a large portion of those to area 8/FC (fig. 9f–i) must have been severed.

Secondary degeneration (figs. 9, 13).—The position of the degenerated fibres on this side differs from that in the left and in fact from that in all the other cases. In the oral-most portion of the internal capsule the entire fibre bundles appear completely normal, and only at Level 2 do a few gliosed fascicles begin to appear in its dorsal sector. These fascicles gradually shift downwards, to occupy

at Level 3 approximately the middle third of the bundles, their ventral convergence being complete only in a much more posterior plane at thalamic Level 4. At the level of the peduncle the heavily gliosed and almost completely demyelinized tract is seen to project downwards in a more lateral position (second fifth) (Plate XIX, fig. 4) than in any of the other cases, leaving, except for a very slight gliosis and demyelination, the most medial tip of the peduncle almost intact. A similar arrangement obtains at the junction of mid-brain and pons, where the bulk of the gliosis is situated within more lateral pontine fascicles, while the small medial fascicles are less involved. The gliosis gradually shifts medio-ventrally to terminate at approximately the same level as on the left side. The pontine cells on this side show pathological changes identical with those on the left. The remainder of the brain-stem is intact. A slight gliosis can be traced into the diencephalic stratum intermedium, but the cells of the substantia nigra, both pars diffusa and compacta appear normal.

No further significant lesion is seen in the remainder of the frontal lobes on either side, nor in representative sections from various parts of the brain.

Case 6.—E. M. was a woman who developed a presenile dementia at the age of 53. She then deteriorated mentally over a period of twelve years. About three years prior to her death she sustained a head injury. There was no evidence of fractured skull or intracranial complications.

General description of the brain.—Macroscopically the brain is small (weight 1,150 grammes) but does not show gross general wasting of the convolutions. The effect of bruising (état vermoulu) is apparent in both frontal poles, more extensive on the left. There are similar small lesions in the right postero-lateral orbital cortex and left temporal pole. Both anterior horns of the lateral ventricle are dilated.

Histologically the cortex presents the typical picture of Alzheimer's presenile dementia with increased lipofuscin in the nerve cells, a number of senile plaques and Alzheimer's neurofibril changes; the glia is moderately proliferated. In addition there are patches of recent cortical paling in the depths of the sulci probably due to anoxia during the terminal disease.

In spite of these diffuse changes the case was included, because of its very circumscribed polar lesions—especially on the right—which are essentially cortical. The present writer is satisfied, that there can be no question of misinterpretation or of confusing the completely demyelinized and gliosed contre-coup lesions of three years' standing with any of the more recent changes in the cortex.

Left Hemisphere.

Cortical lesion (fig. 10a–c).—The injury affects the entire frontal pole to a depth of about 1 cm. It diminishes rapidly in size leaving, at the level of the precallosal part of the gyrus cinguli, the lateral sector of the hemisphere unimpaired and terminating at the level of the genu corporis callosi in a medial position. Areas 10/FE, 9/FDm, 46/FDΔ, the entire anterior orbital and cingular regions are involved. Slight damage to area 45/FD τ is apparent from retrograde degeneration in the dorso-medial nucleus. Figs. 10 and 11.

Secondary degeneration (figs. 11, 13).—Densely gliosed fascicles course through the internal capsule and the medial sixth of the cerebral peduncle (Plate XVI, fig. 1) to end within the antero-medial bundles of the pons (Plate XVII, fig. 1). Their distribution is almost identical with that in Case 1 Left, the only difference being that in the most anterior portion of the internal capsule a narrow lateral margin of the dorsal bundles remains intact. Demyelination throughout the course is slight, but Glees's silver impregnation reveals a considerable reduction in the number of neurofibrils in the medial tip of the peduncle (Plate XIX, fig. 1).

The bulbar reticular formation is intact.

Right Hemisphere.

Cortical lesion (fig. 10d, e).—The damage to the right frontal pole is much

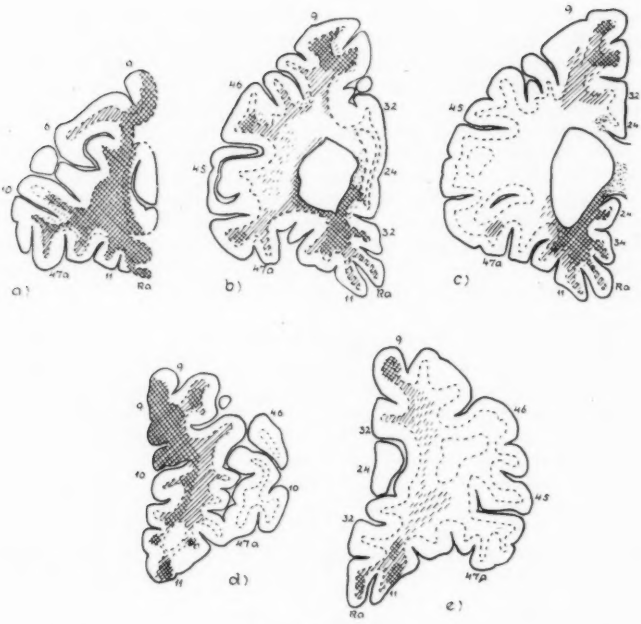

FIG. 10.—*Case* 6.

more circumscribed and superficial than that to the left, and the lesion terminates about 1½ cm. posteriorly to the pole at the level of the tip of the precallosal gyrus cinguli. Apart from its most anterior extremity, the lesion is confined exclusively to the medial half of the hemisphere, and involves area 10/FE and the most oral portion of areas 9/FDm, recta anterior and 11. An additional small focus of état vermoulu is found in the postero-lateral orbital surface. Retrograde degeneration in the dorsomedial nucleus does not reveal evidence of any further damage.

Secondary degeneration (figs. 11, 13).—Serial sections are available from the site of the primary lesion to anterior pontine levels. There is a very slight gliosis in the internal capsule at Levels 1–3, all of which, however, swings medially towards the thalamus at Level 4. Peduncular (Plates XVI, fig. 2, XIX, fig. 2) and pontine (Plate XVII, fig. 1) levels are completely normal, as are the nerve cells around the antero-medial pontine bundles.

Case 7.—L. D. was a woman, who died from lobar pneumonia, aged 66, four years four months after prefrontal leucotomy.

Left Hemisphere.

Cortical lesion (fig. 12).—A small circumscribed lesion, greatest in extent at the level of the genu corporis callosi, occupies the deep white matter of the frontal lobe just lateral to the anterior horn. It diminishes rapidly in an antero-posterior direction involving in its course fibres from areas 46/FDΔ, 45/FDϒ and 47 anterior and some from area 9/FDm. The dorsomedial nucleus shows retrograde degeneration in the corresponding sectors. Fig. 12.

Secondary degeneration.—Gliosis and demyelination in this case are very marked, the degeneration being emphasized throughout by the presence of compound granular corpuscles laden with iron-positive pigment (possibly

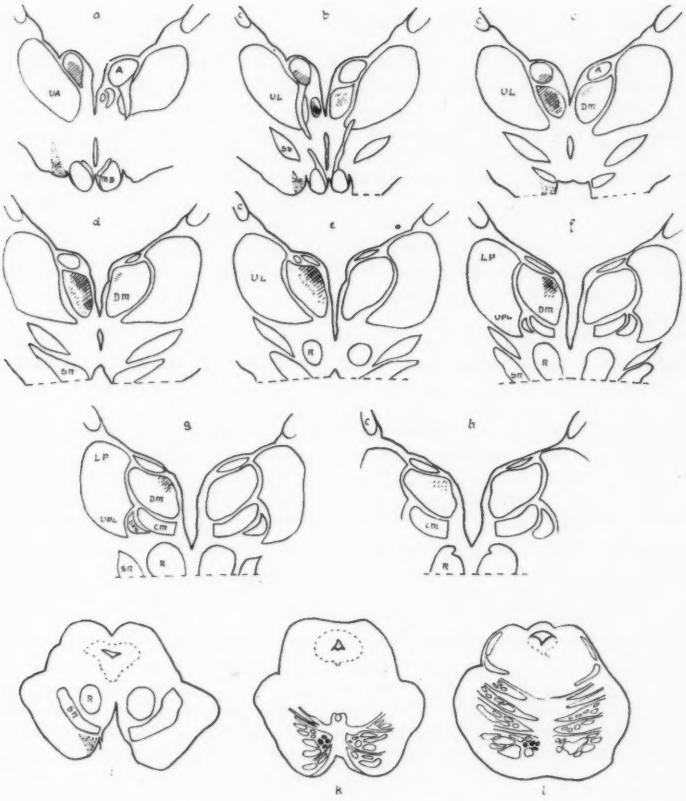

FIG. 11.—*Case* 6.

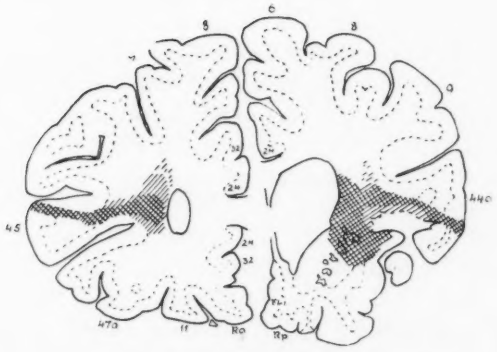

FIG. 12.—*Case* 7.

hæmosiderin). This is a rather unexpected finding not encountered by the present writer in any other leucotomy case. It is possible that it represents the remnants of an unusual oozing of the hæmorrhage from the not very distant leucotomy lesion. The degenerated fascicles can be traced through the internal capsule, where (Levels 1–4) they follow a course in accordance with the site and size of the primary lesion and comparable to that described in all the previous cases. At Level 5, however, the bundle projects into the stratum intermedium pedunculi, where it remains in closest proximity to the substantia nigra throughout the diencephalic portion of this nucleus. It gradually disappears in this position at the level of the anterior extremity of nucleus ruber. The nerve cells of both pars diffusa and compacta appear normal. The medial-most portion of the cerebral peduncle as well as the medial pontine fascicles and nerve cells are completely intact.

Right Hemisphere.

Cortical lesion (fig. 12).—The lesion on this side lies in a much more posterior plane than that on the left, interrupting at the level of the head of the caudate nucleus the pathway taken by the fibres from anterior prefrontal regions. It extends posteriorly for about 9 mm. being situated in the dorsal half of striatum, capsula interna and externa, insula and operculum. From retrograde degeneration in the thalamus it is apparent that it interrupts in this position connexions of areas 9/FDm, 46/FDΔ, 45/FDΥ, 47 anterior and to a lesser extent those of areas 8/FC and 6/FB. (The amount of damage to the latter areas closely resembles that in Case 5 Right.)

Secondary degeneration.—As on the left side the anterior course taken by the degenerated fascicles on the right does not deviate at all from the general pattern so far encountered. The demyelination is almost complete, the gliosis very compact and again interspersed with pigment-laden compound granular cells. At Level 5 the gliosed bundle again remains within the stratum intermedium (Plates XVIII, fig. 2, XIX, fig. 6) in close proximity to the substantia nigra, which is equally intact. The degeneration fades out at approximately the same level—at the beginning of the red nucleus—after having given off two mildly gliosed fascicles, which pass ventrally into the cerebral peduncle proper. These, however, cannot be followed for any distance caudally and never reach the medial-most portion of the peduncle or the medial fascicles of the pons, which appear normal.

Discussion

Whether a *pre*-fronto-pontine tract does, in fact, exist has been disputed in the literature, both for human and for experimental material. Most of the older investigations agree on the presence of such a tract, although its origin is attributed to rather different sites within the prefrontal cortex. In more recent publications, however, and with the application of modern experimental methods the controversy has become more apparent. Mettler (1935) and Levin (1936, 1944), using Marchi's technique, confirm a prefrontal origin of Arnold's bundle experimentally in the macaque brain, the former relating it to area 9, the latter to the anterior portion of the inferior frontal gyrus only. Le Gros Clark (1948) in his review on the connexions of the frontal lobe concurs with the conception of a prefrontal origin of the tract, while Meyer (1949) from human leucotomy material, assumes it to arise anterior to the premotor cortex, but not necessarily from granular prefrontal cortex.

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On the other hand, Kirschbaum and von Bonin (1947), from evidence in a human brain, deny the existence of any fronto-pontine fibres originating anterior to the precentral motor cortex (area 4/Faσ), while Sunderland (1940) and Mettler (1947), in Marchi studies on the macaque brain, delimit the non-contributing zone only to regions anterior to area 6/FB. (The latter author thus does not confirm his earlier (1935) finding.) However, Mettler admits that the Marchi method might not always disclose the existence of very fine myelinated fibres, and although in his experiments no efferent connexions extending caudal to the thalamus were found from prefrontal areas, it is by no means impossible for finer connexions of this type to exist. In view of this statement it should be borne in mind that fibres arising from prefrontal cortex are known to be fine and poorly myelinated, the finer the more anteriorly they originate. Levin (1936) found the anterior limb of the internal capsule almost entirely composed of such fine fibres and Verhaart (1948) encountered similar conditions in the medial part of the peduncle.

Origin of the prefronto-pontine tract.—In Cases 1, 3 and 6 Left, it is verified, both from direct cytoarchitectonic examination and from indirect evidence derived from retrograde degeneration of the thalamus, that the primary lesion definitely terminates within granular prefrontal levels, anterior even to area 8/FC, and that no significant incidental lesion is present in the frontal lobes posterior to the leucotomy cut. Nevertheless gliosed and slightly demyelinized bundles can be traced through the internal capsule and cerebral peduncle to their termination within antero-medial bundles of the pons. These three hemispheres, therefore, provide conclusive proof, that at least a portion of Arnold's bundle originates from purely prefrontal, that is distinctly granular cortex. If furthermore one considers evidence, that fibres from the convexity run obliquely backwards in their course towards the internal capsule—a phenomenon also observed in the macaque by Verhaart and Kennard (1940)—then the number of hemispheres giving support to a prefrontal origin of Arnold's bundle can be extended to include Cases 1 Right, 2 Left and Right, possibly 4 Right and 5 Left in spite of the fact, that their lesions terminate at a level, where the most oral tip of area 8/FC has just appeared on the vertex.

Detailed plotting of areas giving rise to the prefronto-pontine tract is facilitated by the great variability of the lesions in the 6 cases.

Complete absence of degeneration in Case 6 Right excludes from participation to any appreciable degree the frontal pole—area 10/FE—(thus not confirming our earlier tentative suggestion), and the adjoining most oral portions of areas 9/FDm and, on the orbital surface, recta anterior and 11. Furthermore there is some indication from Case 1 that even a

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larger part of areas recta anterior and 11 may be excluded, since gliosis and demyelination are more marked on the right side where these regions are spared, than on the left where they are involved. These findings are borne out by Levin's (1936) experimental results; after ablation of the frontal pole and the medial orbital surface (his experiment 15), he did not find any degeneration in Arnold's bundle. A further region which probably does not contribute any fibres seems to be the lateral orbital surface; Case 4 supports this view, which would tally with Levin's (1936) experiments 16 and 17.

The majority of those fibres constituting the prefronto-pontine tract originate from areas on the lateral as well as on the dorsal aspect of the convexity; the two separate components being well represented in a number of hemispheres: Cases 2 and 3 Left which show, in addition to damage to those regions already excluded from participation, involvement of areas 46/FDΔ and the most anterior portion of areas 45/FDT, 32/FDL and 24/LA illustrate the lateral component of the tract (which is also and even more selectively shown in Case 10 of our earlier publication, where the cingular region is spared). The dorsal component of the tract is clearly indicated by Case 4 Right, which shows an extensive involvement of area 9/FDm with relative sparing of areas 46/FDΔ and 45/FDT. Fibres seem to arise from the full antero-posterior length of dorsal and lateral convexity, since there is a definite correlation between the extent of the surgical lesion and the degree of secondary degeneration in all 6 cases.

A rather complex organization of the medial-most portion of the cerebral peduncle was revealed by Verhaart's (1948) comprehensive study of the fibre architecture of Arnold's bundle in macaca ira. This author described the bundle as composed in the majority of fine fibres, but containing also a number of thick fibres, the latter ending at rostral levels of the pons. After ablation of the precentral area Arnold's bundle appeared essentially intact; after ablation of precentral and premotor areas, however, all its thick fibres and a number of its fine fibres disappeared. These results clearly indicate that in the macaque the majority of the fine-fibred component of Arnold's bundle must be of prefrontal origin, while a smaller portion of the fine-fibred and the entire thick-fibred component arise from area 6 and possibly 8. Such a composition would clarify many contradictory statements of various investigators and thus classify Arnold's bundle as a tract carrying simultaneously prefronto- as well as fronto-pontine components.

Whether similar conditions obtain in the human brain with its very much more highly developed prefrontal region cannot at present be established with absolute certainty; however, there is some indication

that a comparable arrangement exists: Demyelination in the medial one-sixth of the peduncle is never complete in any of our 6 cases, and even in Case 5 Left with its very substantial lesion of prefrontal regions a considerable number of fibres appear intact. On the other hand, in Case 5 Right, where the greater part of the prefrontal cortex is spared and a posterior lesion interferes mainly with projections from dysgranular and agranular areas, the medial one-sixth of the peduncle shows slight degeneration. If, however, a lesion involves simultaneously all the regions mentioned above, then demyelination in the medial tip of the peduncle is complete. Fig. 13.

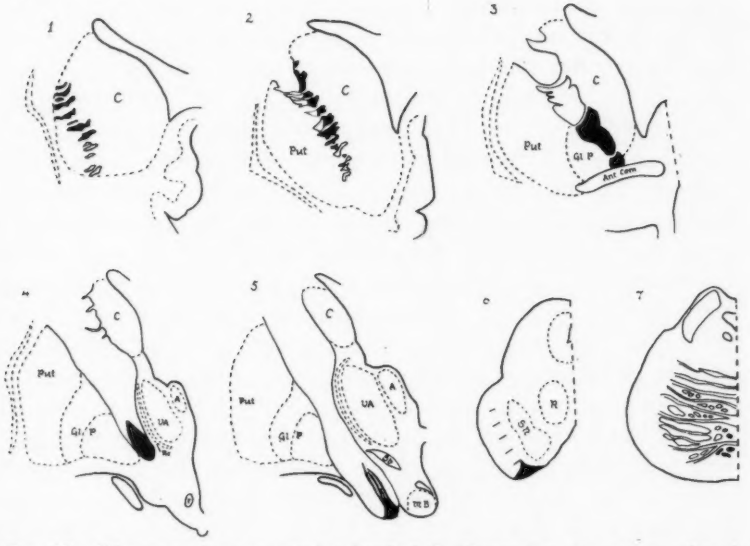

FIG. 13.—Diagram of representative levels 1–7, illustrating the course taken by the prefronto-pontine tract (black areas), which originates from granular areas 46/FD Δ, 45/FD ϒ and 9/FDm. At level 6 the cerebral peduncle, having reached its full width, has been divided into sixths, the medial-most of which contains the tract.

Course and termination of the prefronto-pontine tract (fig. 13).—The course taken by the prefronto-pontine tract is essentially identical in all the 6 cases and agrees entirely with our description given in 1947 (cf. fig. 19) and with Levin's in 1936 for the macaque. The tract is outlined throughout its length by a clearly defined and sharply circumscribed gliosis and demyelination, varying in intensity according to the size of the cortical lesion. A very minute spatial organization seems indicated by slight variations from case to case. Thus, apart from the well-known antero-posterior orientation within the internal capsule, it seems that

fibres from the lateral convexity run in the lateral half of the dorsal bundles, while fibres from the dorsal convexity occupy the medial half of these same bundles (cf. Cases 4 Right, 6 Left). The ventral half of the internal capsule is taken up by thalamo-frontal fibres projecting upon the orbital cortex and possibly does not carry any prefronto-pontine component (cf. Case 4 Right). As soon as the bundles converge—at the level of the anterior tip of the globus pallidus—the fibres from the different areas intermingle, so that it is not possible any longer to separate distinct sectors. Within the cerebral peduncle[1] the size of the degenerated area, described quite differently by various investigators, varies in proportion to the extent of the lesion: In none of the purely prefrontal cases is the full size of the classical "medial fifth" attained and the area is more approximately a medial sixth. As soon as dysgranular area 8/FC participates, this medial sixth is exceeded (Case 4 Left) and with a more extensive involvement of area 8/FC and anterior area 6/FB the full fifth is reached. Levin (1936) has shown a similar arrangement for the macaque, confirmed for the human brain by Meyer (1949). At the junction of mid-brain and pons the bundle occupies the small medial pontine fascicles, terminating apparently on the surrounding nerve cells, many of which display transneuronal degeneration. It can be followed for a short distance (approximately 10 mm.) caudally, shifting ventrally in its course, the number of degenerated nerve cells diminishing in proportion to the decrease of gliosis. A certain antero-posterior relationship seems indicated: In Case 1, with the more anterior lesion, the degeneration terminates at the level of the trochlear nerve decussation, in Case 5 slightly more posteriorly at the level of the caudal extremity of the trigeminal motor nucleus. In none of the cases could the degeneration be followed into lower levels of the pons or into the bulbar reticular formation as described by Ward (1948) following lesions of the cingular region. It seems, however, possible that the scattered degenerated fibres observed by this author might not cause a glial reaction distinct enough to be noticeable with the comparatively crude method employed in this study. The question of a contribution from the cingular suppressor zone to the prefronto-pontine tract in man must therefore remain open.

In none of those cases with purely prefrontal lesions can any gliosis be traced into the *stratum intermedium pedunculi*, the *substantia nigra* or the *reticular formation of the mid-brain*, although the degenerated

[1] In only one of our cases (Case 2) is the "medial angle" of the peduncle free from degeneration. Mettler (1947) places the cortico-bulbar tract, known to be derived from areas 4/FAσ and 6/FB, in this position, other investigators, however, show its fibres interspersed in the middle segment and draw attention to the great variability of this system.

tract runs closely adjacent to these structures throughout the length of the cerebral peduncle; nor can any degenerated nerve cells be found in either pars diffusa or compacta of the substantia nigra. These observations are in complete agreement with the now generally recognized view, that the cortico-nigral system arises exclusively from agranular frontal cortex.

Degeneration of a *cortico-mesencephalic-tegmental tract* as described by Levin (1936) after ablation of prefrontal areas in the inferior frontal gyrus could not be seen in any of our cases. This tract, however, seems to be rather inconstant; e.g. it was found in only one out of three of Levin's cases. The same conditions seem to apply to the *cortico-tegmental tract,* which according to Levin carries a small very fine-fibred component from prefrontal regions, but could not be seen in the present material.

Individual variation.—Amongst 33 cases available for comparative investigation, 32 show a degeneration of the prefronto- and/or fronto-pontine system, which follows in course and distribution almost precisely the general pattern of organization outlined above. Case 7, however, differs considerably. The lesion on the left is confined to fibres from prefrontal areas, while on the right it involves those from prefrontal and premotor areas; the cortex of these areas shows no obvious cytoarchitectonic abnormality. A very marked and dense secondary gliosis and demyelination is present, which throughout anterior levels follows a course comparable in its distribution with the rest of the cases. At Level 5, however, where the bundle usually enters the cerebral peduncle, passing on its way through the stratum intermedium, the gliosis is confined, in the left as well as in the right hemisphere, to the stratum intermedium, where it fades out at the level of the beginning of nucleus ruber. The degeneration never reaches the medial part of the cerebral peduncle and cannot be traced to any more caudal levels. Considering the site of the primary lesion, especially in the right hemisphere, the conclusion is almost unavoidable that fibres from both the prefronto- and fronto-pontine system ought to have been interrupted. Evidence from several cases with almost identical cortical lesions would lead one to expect in the left hemisphere: a marked gliosis in peduncle and pons, but none in the stratum intermedium; in the right hemisphere: a compact gliosis with complete demyelination in both these structures. (Plates XVIII, fig. 1, XIX, fig. 5 illustrate one of these cases.) This gliosis in the stratum intermedium is considered to be associated with degeneration of the cortico-nigral tract known to arise from area 6/FB.

The question of a possible inadequate staining reaction has been carefully examined, but it seems unlikely that in a case where other systems stand out compactly gliosed and demyelinized after a survival period of

more than four years, the prefronto- and fronto-pontine systems should not show the slightest trace of degeneration. One therefore must arrive at the tentative conclusion, that in Case 7 a prefronto-pontine system does not exist and that the fronto-pontine system is either equally absent or is derived exclusively from posterior parts of area 6/FB and/or the precentral motor cortex. An interpretation of the degenerated appearance of the left stratum intermedium cannot be given at the present juncture.

It seems possible that Kirschbaum and von Bonin (1947) in their human case were dealing with a similar anomaly. Theirs was a case with extensive damage to prefrontal and premotor areas on both sides and they did not observe any degeneration in the cerebral peduncles or pons. They arrived at the conclusion, that the fronto-pontine tract arises exclusively from the precentral motor cortex, a conclusion which could be explained in the light of the case just described.

That the fronto-pontine system is liable to individual variations is also shown by the occurrence of aberrant bundles passing through the subthalamic nucleus on their way to more caudal levels. Winkler (quoted by Whittier and Mettler, 1949) and Meyer, Beck and McLardy (1947) reported 3 such cases in human material while Kodama (1927) observed the same phenomenon in dogs. These aberrant fascicles invariably proceeded into the cerebral peduncle and usually could be followed into the pons.

Experimentally individual variation has been observed by Verhaart (1948) in his study on the normal fibre architecture of Arnold's bundle in the macaque. He found that the number of fibres of different calibre varied greatly from case to case, amounting, according to his tables, in some instances to a difference of as much as 50 per cent. It would be tempting to presume, that similar individual variations might occur in the human brain.

Summary

(1) Six cases have been presented showing circumscribed, essentially prefrontal lesions, a fact confirmed by cytoarchitectonic examination. They have been compared with 22 further cases, in many of which the lesion includes anterior portions of area 6/FB.

(2) The existence of a prefronto-pontine bundle arising from granular prefrontal cortex has been established in three hemispheres, in which the primary lesion terminates at a level anterior even to the dysgranular area 8/FC and where the entire frontal lobe posterior to the leucotomy cut is free from any significant incidental lesion. In these 3 cases the degenerated tract can be traced through the internal capsule and the medial portion of the cerebral peduncle to its termination within the medial fascicles of the pons. The nerve cells surrounding these fascicles

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display transneuronal degeneration. All but one of the remaining 25 cases show degeneration of the prefronto-pontine and/or fronto-pontine tracts.

(3) The prefronto-pontine tract is shown to be derived from the dorsal as well as from the lateral convexity of the prefrontal region. The extreme pole and the entire orbital surface do not contribute.

(4) The question whether the cingular suppressor area contributes to the prefronto-pontine tract cannot be decided on the present material.

(5) A certain overlap of thicker fibres from dysgranular and agranular areas seems to exist in Arnold's bundle, which would therefore be better classified as a tract carrying simultaneously prefronto-pontine as well as fronto-pontine components. This is in agreement with experimental evidence in the literature.

(6) The size of the degenerated area within the cerebral peduncle varies in proportion to the extent of the lesion from a medial one-sixth in those cases with exclusively prefrontal involvement to a medial one-fifth in those with additional damage to anterior agranular zones.

(7) No cortico-nigral fibres originate anterior to area 6/FB.

(8) It is suggested that individual variations may exist regarding the fibre composition of the fronto-pontine system. One case with complete absence of at least the anterior component of this system is described in detail. A bilateral occurrence of this and similar anomalies has been noted.

ACKNOWLEDGMENTS

I wish to express my gratitude to Professor A. Meyer for his criticism and guidance in this study; to Dr. Turner McLardy for cross-checking some of the anatomical data; and to Hilda Cox for her skill in providing the innumerable slides.

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LIST OF ABBREVIATIONS USED IN FIGURES

A	=	Nucleus anterior thalami.
Ant. Com	=	Anterior commissure.
C	=	Nucleus caudatus.
CM	=	Nucleus centrum medianum.
DM	=	Nucleus medialis dorsalis thalami.
F	=	Fornix.
Gl.P.	=	Globus pallidus.
LP	=	Nucleus lateralis posterior thalami.
MB	=	Corpus mammillare.
Put	=	Putamen.
R	=	Nucleus ruber.
Ra	=	Area recta anterior.
Ra/p	=	Area recta anterior/posterior.
Re	=	Nucleus reticularis thalami.
Rp	=	Area recta posterior.
Sb	=	Corpus subthalamicum.
SN	=	Substantia nigra.
VA	=	Nucleus ventralis anterior thalami.
VL	=	Nucleus ventralis lateralis thalami.
VPL	=	Nucleus ventralis postero-lateralis thalami.
VPM	=	Nucleus ventralis postero-medialis thalami.

LEGENDS FOR PLATES

PLATES XVI AND XVII

Photomicrographs of the degenerated prefronto-pontine tract, taken from cases in which the primary lesion is confined to granular prefrontal areas. Nissl stain, × 13.

PLATE XVI, FIG. 1.—Gliosed fascicles are seen to pass into the medial tip of the cerebral peduncle. (Case 6, Left, Level 5/6.)

FIG. 2.—Normal appearance of the cerebral peduncle; primary lesion confined to the extreme frontal pole. (Case 6, Right, Level 5/6.)

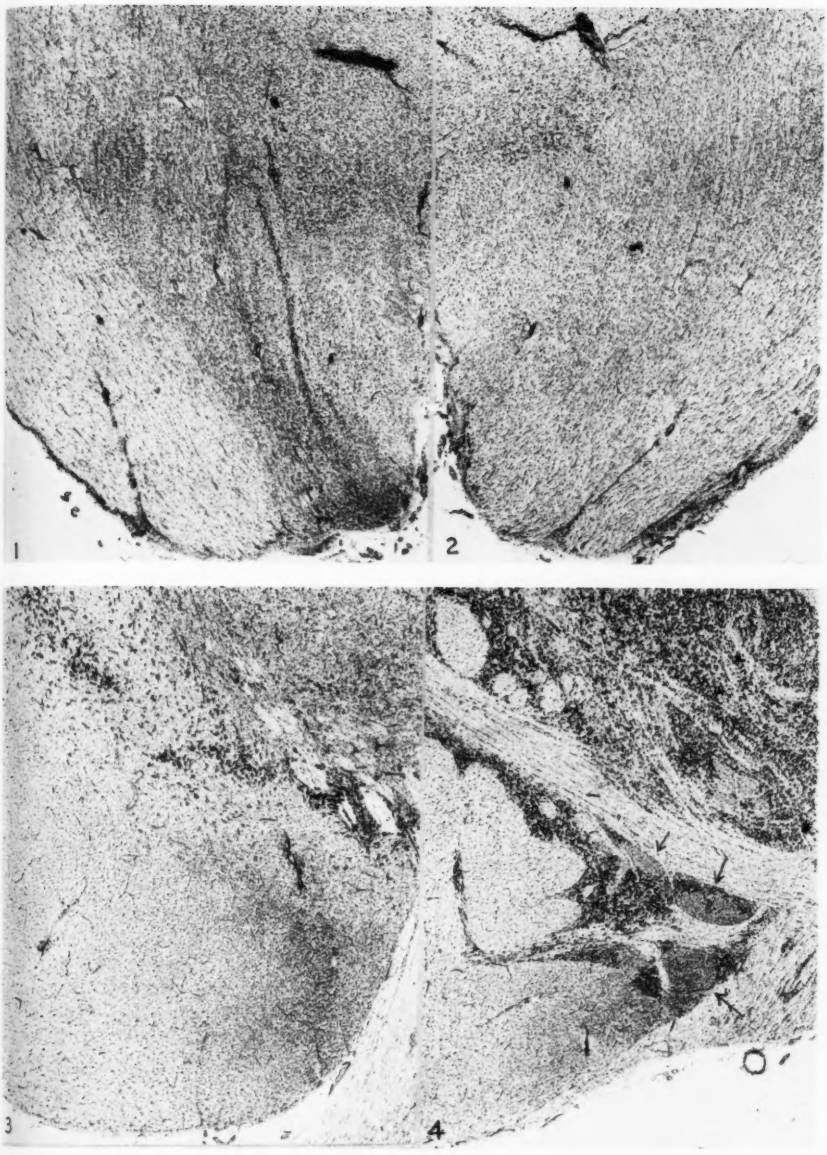
FIG. 3.—The gliosed bundle is situated within the medial one sixth of the cerebral peduncle. (Case 1, Left, Level 6.)

FIG. 4.—The gliosis has split up and is now situated in the small medial fascicles of the pons (arrows). (Case 5, Left, Level 6/7.)

PLATE XVII, FIG. 1.—The gliosis is situated exclusively in the left small ventromedial fascicles of the pons (arrows), the larger lateral bundles being intact. The right side appears normal throughout. (Case 6, Level 7.)

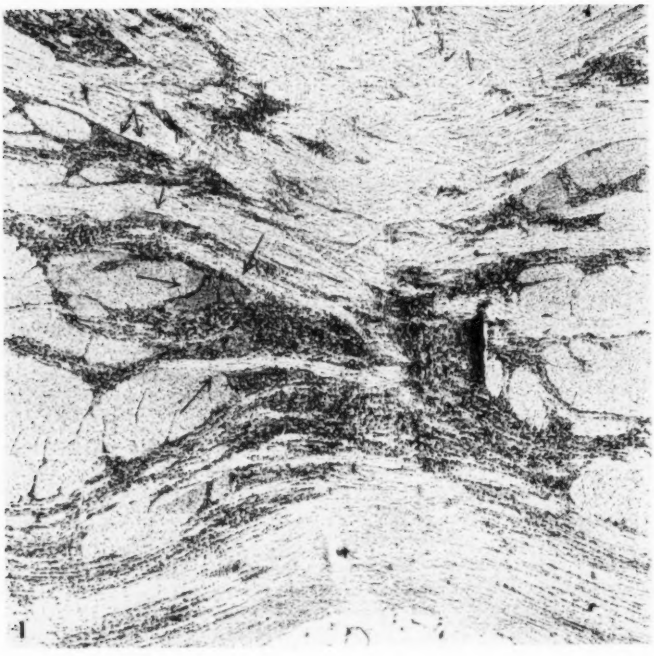
FIG. 2.—Pontine nerve cells showing transneuronal degeneration are situated between two degenerated fascicles. Some cells of normal size and appearance are seen on the left of the photograph. × 220. (Case 5, Left, Level 7.)

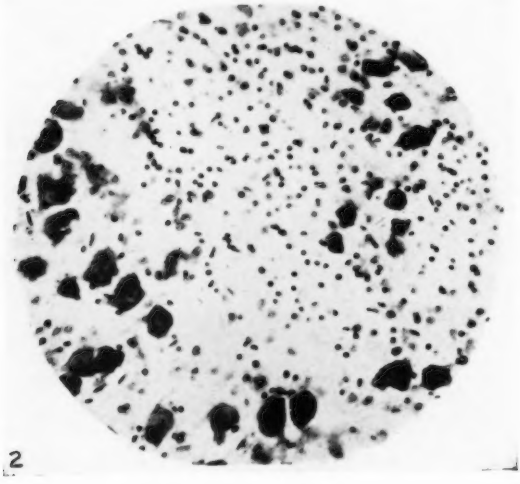
PLATE XVI



To illustrate article by Elizabeth Beck.

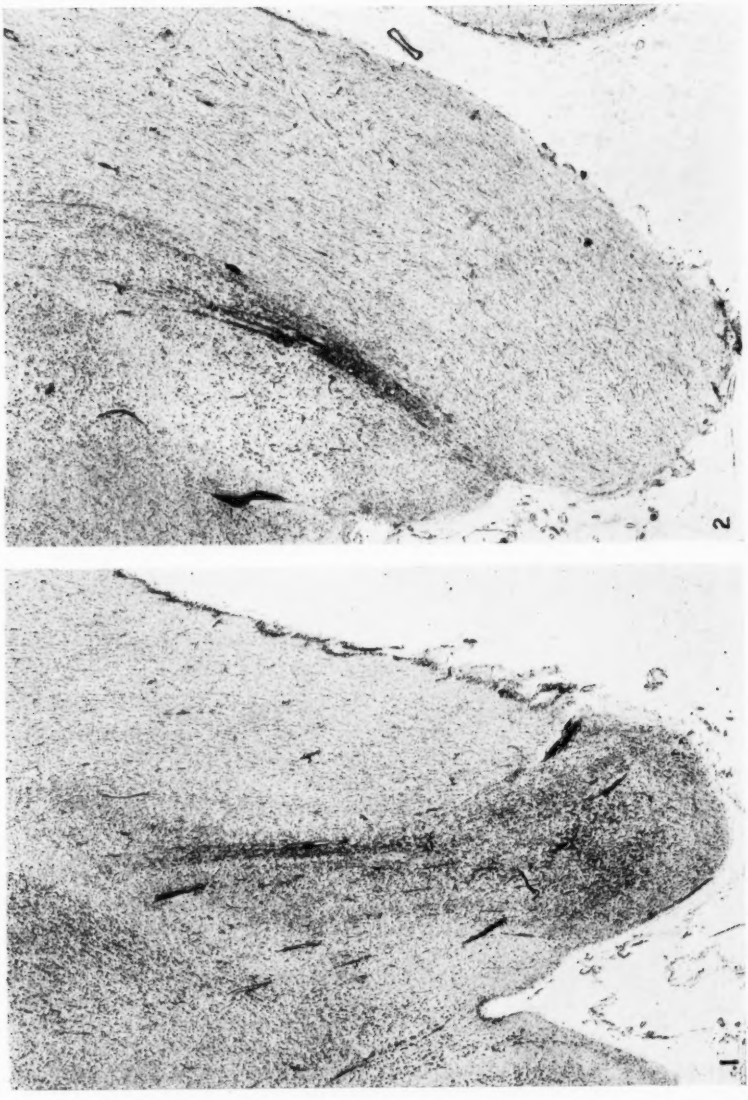
PLATE XVII





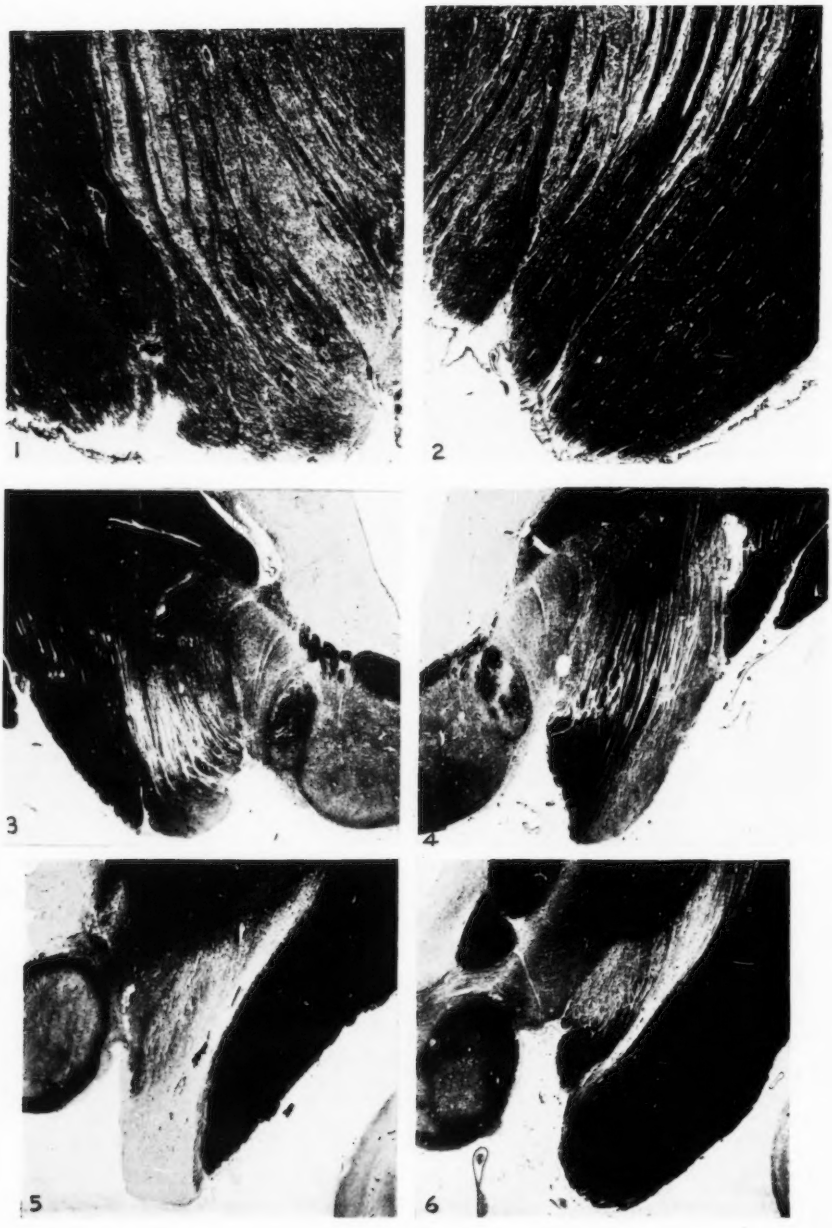
To illustrate article by Elizabeth Beck.

PLATE XVIII



To illustrate article by Elizabeth Beck.

PLATE XIX



To illustrate article by Elizabeth Beck.

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PLATE XVIII

Photomicrographs of corresponding levels in two different cases with very similar primary lesions involving prefrontal and premotor areas. Nissl stain, × 13.

FIG. 1.—An area of massive gliosis, considerably larger than in Plate XVI, fig. 1, occupies the medial portion of the cerebral peduncle. The stratum intermedium is also affected. (Right Hemisphere, Level 5/6.)

FIG. 2.—The gliosis is confined to the stratum intermedium; the medial portion of the cerebral peduncle being completely intact. (Case 7, Right, Level 5/6.)

PLATE XIX

FIGS. 1 and 2.—Photomicrographs of corresponding levels in the left and right cerebral peduncle of Case 6, in which the primary lesion is confined to granular prefrontal areas. Glees' silver impregnation for neurofibrils, × 22. The medial tip of the peduncle on the left side (fig. 1) shows a considerable reduction in the number of neurofibrils in comparison with the normal right side (fig. 2). There is also a marked difference in the size of the fibre bundles passing through the diffuse portion of the substantia nigra; those on the left side appearing rather scanty.

FIGS. 3 to 6.—Photomicrographs of Level 5/6 in four different hemispheres with primary lesion in prefrontal and/or premotor regions. Heidenhain modification of Weigert's method, × 4·4.

FIG. 3.—Marked demyelination of the medial tip of the cerebral peduncle subsequent to a lesion of almost the entire prefrontal areas. The preserved fibres are probably derived from area 6/FB. (Case 5, Left.)

FIG. 4.—The medial tip of the cerebral peduncle is intact while an adjacent lateral strip is almost completely demyelinized. The primary lesion in this case spares prefrontal projections, but interrupts fibres from areas 8/FC and 6/FB. A slight demyelination obvious under the microscope is not very well brought out by the photograph. (Case 5, Right.)

FIG. 5.—The medial portion of the cerebral peduncle is completely demyelinized owing to lesion of prefrontal as well as dysgranular and anterior agranular regions. The size of the affected area approximately equals that of figs. 3 and 4 combined. The stratum intermedium is also demyelinized. (Right Hemisphere.)

FIG. 6.—The cerebral peduncle is completely intact and demyelination is confined to the stratum intermedium, although the primary lesion is very similar in extent to that shown in fig. 5. (Case 7, Right.)

ELECTROENCEPHALOGRAM IN SUBACUTE PROGRESSIVE ENCEPHALITIS

BY

WILLIAM COBB and DENIS HILL

(*From the National Hospital and the Institute of Psychiatry, London*)

DURING the past three years the writers have observed the electroencephalograms of five patients during illnesses diagnosed as subacute encephalitis. The earliest of these (M. J.) was described by Russell Brain, Greenfield and Dorothy Russell (1948). Study of the brain of this patient revealed inclusion bodies within the cells of the cortex and optic thalamus, indicating that the disease was of the type described by Dawson (1933) and called by him "inclusion encephalitis." Two further cases (B. H. and S. C.) are reported by Greenfield (1950) in the present journal. The brains of both these patients also showed inclusion bodies in the cells of the cortex, and elsewhere. The brain of a fourth case (J. D.), a patient in the Maudsley Hospital, has been studied in the department of Professor A. Meyer and will be reported on elsewhere. No inclusion bodies were found and the type of encephalitis was regarded as that described by Van Bogaert (1945). A fifth case (S. F.), also a patient in the Maudsley Hospital, is still alive after two and a half years of illness. The clinical diagnosis of subacute encephalitis has been confirmed by a biopsy which, however, did not permit a decision about the type of disease to be reached.

The electroencephalograms of these 5 patients showed, at some stage of the illness, common characteristics which can be so easily recognized as to suggest the diagnosis. Only one record was obtained in the case of M. J., three months before death (fig. 1). B. H. had eleven records taken over six weeks, death occurring two weeks after the last record. S. C. had two records taken six and five weeks before death. J. D. had three records taken during her illness which lasted five months, the last being a month before death. S. F., in hospital for over two years, has had records taken throughout the period.

Case history (Dr. Denis Leigh).

S. F., aged 14, a schoolgirl, was admitted to the Maudsley Hospital on 22.12.47 with a ten months' history of difficulty in concentration, lassitude, drowsiness and insomnia. Her weight had increased over this period, and ten days prior to admission she had developed an excessive thirst. On 15.12.47 she became excited and restless, and stated that she could hear the voices of children outside her

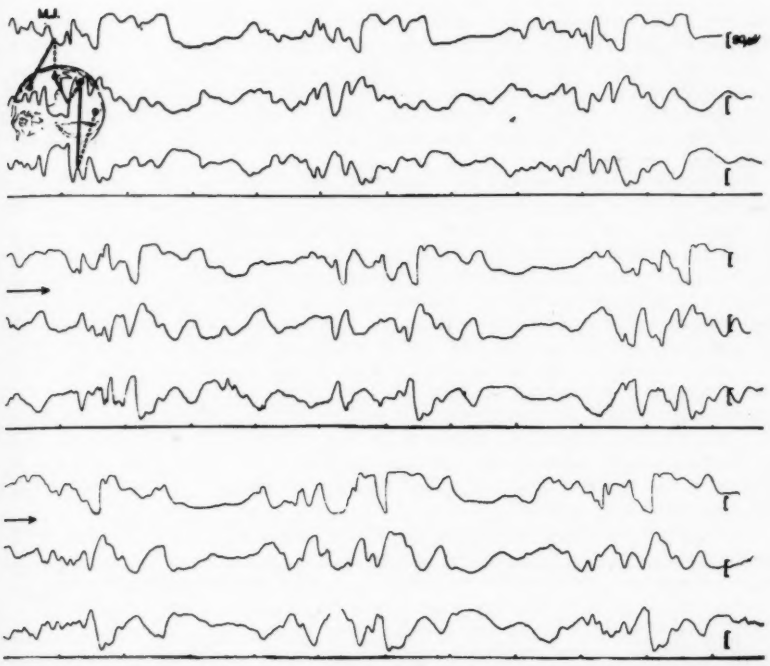

FIG. 1.—M. J., aged 6. Only one record was obtained from this child, the first of the series, and its nature was not recognized until comparison with those of the later cases was possible. The figure shows three sections of record which are continuous, and includes nine complexes in 36 seconds; 4 seconds was the shortest mean interval observed in any of the cases. Phase relationships indicate a predominantly post-central origin for these slow waves and, although the complexes are not strictly repetitive, common features can be recognized, particularly the very sharp fronted wave which is 180 degrees out of phase in channels 1 and 3.

window, calling her; she had a mild epistaxis on this date. Her family and personal histories revealed nothing of significance. She had been a normal child of superior ability, of happy sociable disposition. Apart from measles and bronchopneumonia at 10 months and later tonsillitis and mumps, she had been healthy. On admission her optic discs and fundi were normal; the pupils were equal and reacted to light and accommodation. There was a left facial weakness. All tendon-jerks were brisk and equal. The plantar responses were flexor. No abnormality was found in any other system. Her temperature was 98·4° F., her pulse-rate 70/minute. She was restless, frequently attempting to get out of bed. She appeared suspicious and apprehensive, but at times broke into a laugh or smile for no apparent reason. Her appetite was voracious. She was disorientated in time and place, and showed a memory defect for both recent and past events. There was marked perseveration. Visual and auditory hallucinations were noted. Psychological tests revealed a marked deterioration in mental function. On 2.1.48 her EEG revealed an abnormal record. There were occasional delta waves at 2–3 c/sec. seen mainly from the right hemisphere. The greatest abnormality was seen from the temporal and central areas. Traces of normal alpha and beta rhythms were also present. Overbreathing caused high voltage 1½–2 c/sec. delta activity to appear

from the right hemisphere, and to a far lesser extent from the left hemisphere. "This record is compatible with the diagnosis of organic deterioration and suggests a right-sided space-occupying lesion, probably temporal" (fig. 2). At lumbar puncture the pressure was 200 mm. of C.S.F. and the protein content 30 mg. per cent; there was a trace of globulin, the Lange reaction was of paretic type—5432100000, and the Wassermann reaction in C.S.F. and blood was negative. X-ray of the skull was normal.

On 20.1.48 the EEG showed an increase of abnormality (fig. 2). Right fronto-temporal activity of higher voltage and lower frequencies was present. On 23.1.48 she was transferred to the National Hospital for pneumoencephalography which showed no abnormality of the ventricular system. On 22.2.48 she had a brain biopsy, and later histological examination showed changes consistent with a diagnosis of subacute encephalitis. She was readmitted to the Maudsley Hospital on 17.3.48, now showing evidence of severe mental deterioration, and both plantar responses being extensor. The EEG (30.3.48) was reported on as follows: "The maximal disturbance appears to be in the right temporal and central areas, but now the delta activity is less localized, and the left hemisphere is involved generally. The periodic high voltage slow potentials are still present and are accompanied by a jerk—the left shoulder being mentioned by the recordist. It would appear that the lesion has now become more generalized and there is no local increase of severity at the original focal site. This favours the diagnosis of encephalitis in preference to that of tumour" (fig. 2).

Her clinical condition became progressively worse and on 10.4.48 choreiform

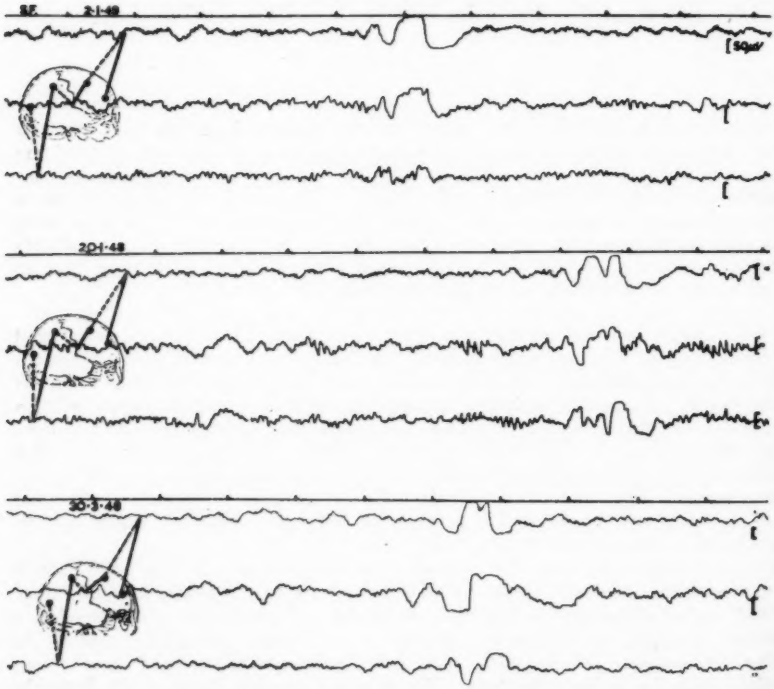

FIG. 2.—S. F. Records covering a period of three months to illustrate the decline in normal activity as the disease advances. Only one complex is shown at each date.

movements of the hands and upper limbs, together with facial tics and grimacing, were noted.

On 13.4.48 the EEG was reported again: "Progressive deterioration in this EEG which is now grossly abnormal, but more so on the right side. Some alpha activity still apparent from the left cortex. The repeated complex discharges increasingly resemble the discharges seen in recently examined cases of subacute encephalitis." On 25.5.48 the EEG showed: "Progressive further deterioration in the EEG, decline in amplitude and decrease in frequency with general disorganization. No normal rhythms. Episodic disturbances still seen."

Her clinical condition varied from drowsiness to motor restlessness and excitability with elation, and it was difficult to keep her in bed. Early in June she developed attacks characterized by extension of the head and neck with opening of the mouth; on 6.6.48 she had her first major convulsion, while minor attacks continued almost daily. On 30.8.48 the episodic discharges in the EEG had become very similar to other cases of subacute encephalitis, and were showing a tendency to be periodic. The tics continued with the added movement of protruding the tongue. The left arm was slightly weaker than the right.

Slow improvement followed and she became quieter but rather euphoric. She showed increasing awareness and named a nurse correctly, also producing the correct names for objects. She would hold a book in her hand but could not read. The abnormal movements persisted and a tremor of the left hand developed by November. She had lost about one stone in weight in nine months and remained apyrexial throughout. During December 1948 she had at least two major fits followed by a period of slight general improvement in the next two months, the movements being reduced in extent. They were observed about this time to be recurring every 6 to 10 seconds.

By January 1949 she was again taking food well and calling people by name. An increasing emotional lability with frequent temper tantrums accompanied this improvement (fig. 3). In the autumn and towards the end of 1949 she became increasingly silent and drowsy. Barbiturates were withdrawn and amphetamine sulphate was tried without effect. Drowsiness persisted. She was unable to talk or to recognize her parents. A transient left facial weakness appeared, together with increasing spasticity of the lower limbs, and a rise of temperature in the evening to about 99°–100° F. Menstruation, which had commenced about the time of admission and proceeded regularly, stopped completely.

At the present time, February 1950, she lies mutely in bed, in a posture of decerebrate rigidity. At times the reflex changes described by Magnus and de Kleyn can be obtained. She swallows food placed in her mouth but is incontinent of urine and fæces.

In 3 patients, B. H., J. D., and S. F., sufficient numbers of records were obtained over a period to allow recognition of progressive changes in the EEG, consisting of the disappearance of normal rhythm and the development of a repetitive complex of high voltage slow waves, having paroxysmal occurrence and showing a tendency to periodicity as the disease progressed. In the early stages of the disease in these cases, in one before the paroxysmal complexes were observed, single spikes and other disturbances of the type found in the records of epileptics, were seen in the frontal regions. Later, the occasion of each slow-wave complex was preceded by irregular slow activity. Still later the complexes occurred without the preceding frontal area disturbance. Each complex consisted of a group of high voltage slow waves, and was followed by a period of a

FIG. 3.—S. F. About one year later than fig. 2. The two strips of record are continuous and show eleven complexes in 82 seconds. Note that the progress of this girl's illness was not steadily downward and, although the intervals between complexes have decreased, there is some return of normal activity.

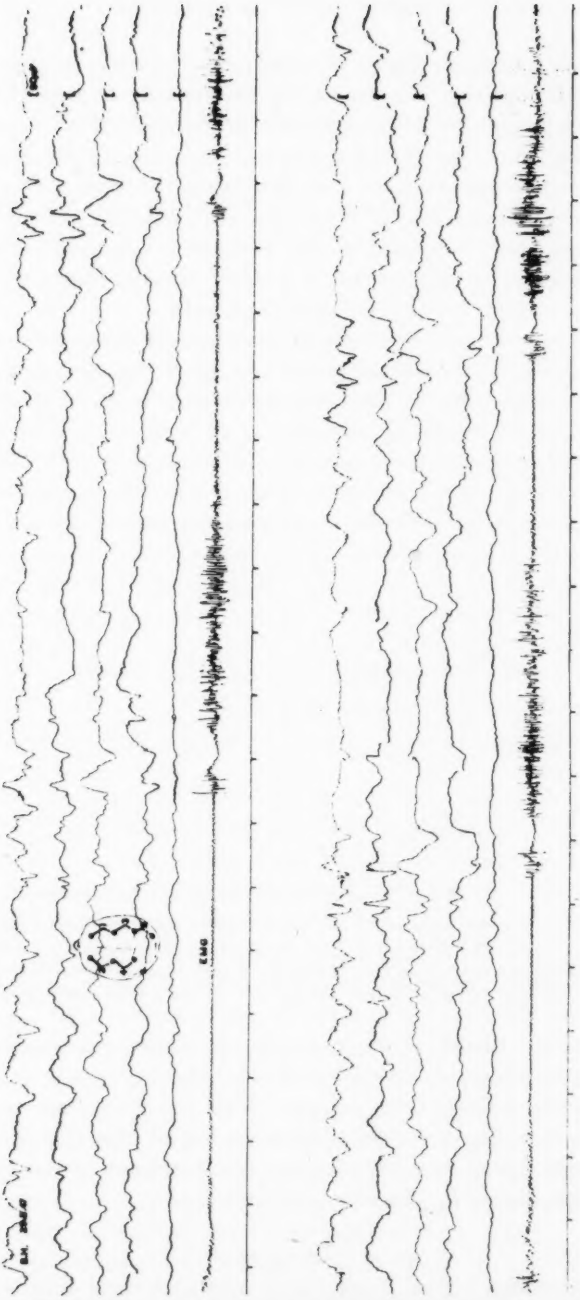

FIG. 4.—B. H., aged 9. An electromyogram recorded from surface plates on the left forearm indicates the relationship of the motor activity to the cerebral slow waves. Frontal spikes are also shown.

few seconds relative absence of activity from the record. During this period of electrical inactivity, the involuntary movements and altered tone of the patient's musculature, initiated during the complex disturbance, was continued (fig. 4). This complex slow activity, having become periodic, repeated at intervals of from 4 to 20 seconds, the intervals varying from record to record and patient to patient. For example, the mean interval for one case was 7·3 seconds on one occasion, the variation being from 5 to 8·5 seconds. In another case, the mean intervals measured at weekly tests were 9·4, 8·0, 10·5, 9·2, 8·4 and 8·7 seconds.

While on the occasion of any examination the waves in each complex usually retained a striking constancy of form (fig. 5), there was great variability from time to time and even more from subject to subject. However, the characteristic common to all occasions and to all patients was the periodicity of the phenomena (fig. 3).

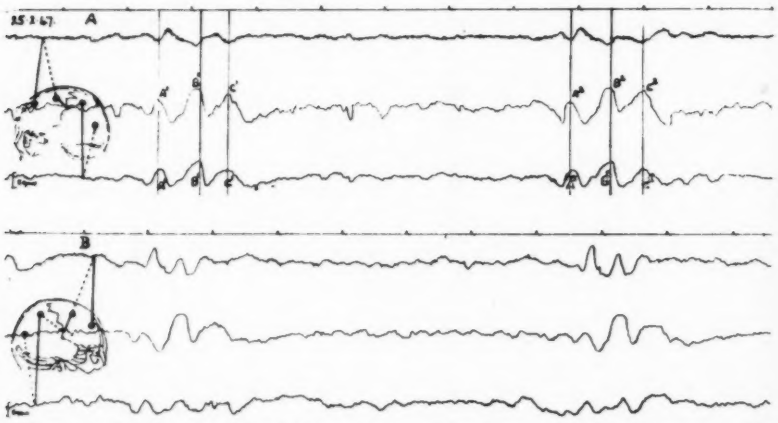

FIG. 5.—J. D.; this girl of 19 was in a rather later age-group than the other 4 cases, but her EEG shows changes very similar, for example, to those of B. H. (fig. 6), a child ten years younger. As in fig. 6 this figure shows well the remarkable constancy of form possessed by the complexes in their fully developed state.

Within the periods in which the fatal cases were under observation, so far as could be judged, the amplitude of all activity, normal and abnormal, progressively declined. In the case of B. H., the records before death showed an absence of rhythm, broken periodically by the groups of slow waves, each group forming, as already indicated, a complex having remarkable constancy of wave-form (fig. 6).

DISCUSSION

The periodic "burst" potentials of subacute encephalitis are a phenomenon rarely encountered in clinical electroencephalography. The writers

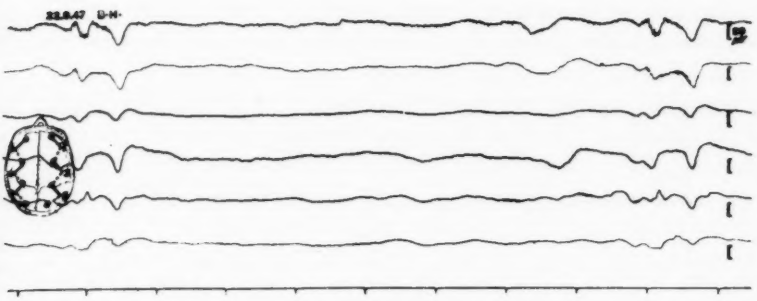

FIG. 6.—B. H., three and a half weeks before death, showing two highly stereotyped complexes, with an almost complete absence of intervening activity. Compare with fig. 4, an EEG from the same subject twenty-four days earlier.

have not met them in any case of intracranial space-occupying lesion, nor following trauma of the brain, nor in patients suffering from toxic or diffuse degenerative disorders. Reports of the EEGs of patients suffering from the commoner forms of epidemic virus encephalitis do not indicate similar phenomena in them (e.g. Gibbs and Gibbs, 1947). However, while this paper was in preparation, Rademecker (1949) published his findings in three of Van Bogaert's cases. The descriptions and illustrations of the records leave no doubt that they are similar to those described here. Through the courtesy of Dr. R. Hess of Zurich, we have also seen the EEG record of a similar case under his care, in which the characteristic repetition occurs.

There is, however, one transient state of disorganisation of brain function which gives rise to EEG changes which bear striking resemblance to those under discussion. This is the unconscious state which follows upon the cessation of the generalized epileptic seizure. For varying periods up to a minute, following the end of the clonic stage of the seizure, no rhythmical activity may be seen in the EEG. Then a burst of slow rhythmical waves is seen, followed by a period of electrical inactivity, and followed again by a further burst. The bursts of slow waves, which are of high voltage, then recur with an obvious periodicity, the intervals between them showing little activity. The periods between the bursts gradually become shorter and the number of waves in each burst greater, until finally continuous generalized slow activity is apparent in all areas. However, even when the occipital alpha rhythm has reappeared, a tendency for periodic occurrence of the slow waves may be seen. These changes parallel the gradual return of consciousness (fig. 7). If these phenomena are considered in reverse they resemble, on a time-scale of minutes compared with weeks, the changes seen in the EEGs of patients suffering from subacute encephalitis.

XUM

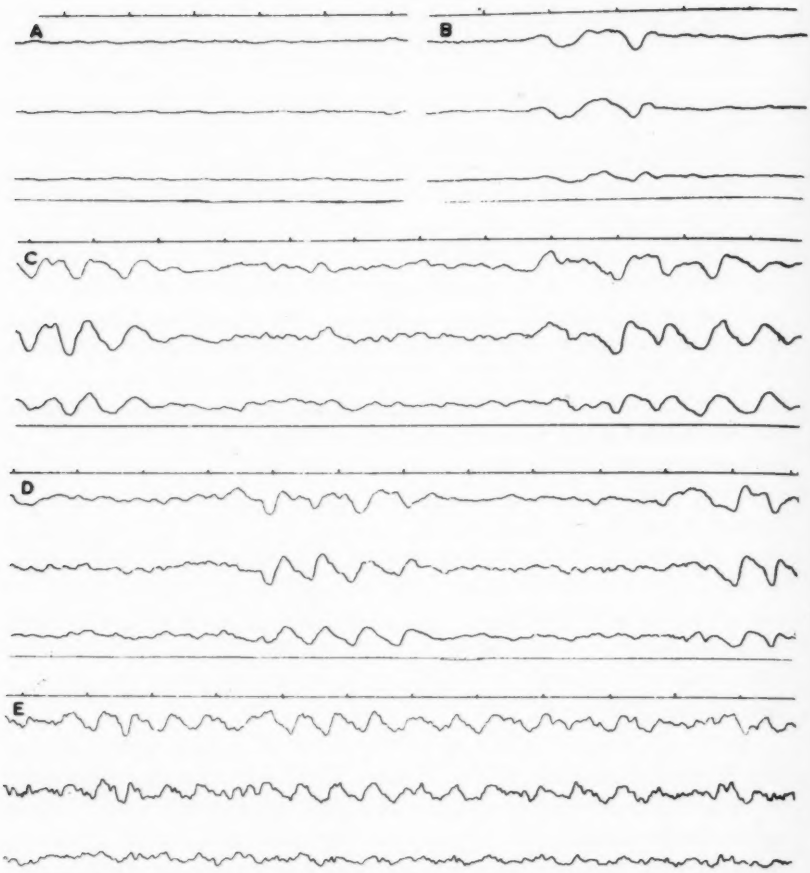

FIG. 7.—The EEG of a patient *following* an electrically induced convulsion, under curare: A, immediately after the attack the EEG is quite flat. B, 15 seconds later the first group of slow waves appears. C and D (which are continuous), 45 seconds after "B" large slow waves are recurring in bursts, the intervals between which will become steadily shorter until in E, after a further twelve minutes, these waves are continuously present. There is also a steady increase in normal and in intermediate slow activity; the slowest waves will ultimately subside until the record approximates to the pre-convulsion state.

Recognizable complexes having stereotyped form, recurring in the EEG, are, as we have mentioned, rare, with the exception of the wave and spike of epilepsy. In the cases described, the association with a common pathological condition makes the phenomenon of exceptional interest, not only because of its diagnostic value. Nevertheless, the latter must be emphasized, since in two cases the EEG records were immediately identi-

fied as resembling those of earlier cases. In considering the possible factors responsible for the development of these periodic changes, a number of alternatives present themselves. It seems unlikely that a biochemical disturbance of systemic or intracerebral origin could produce periodicity of this order, although phases of rhythmical activity followed by relative "silence" are seen associated with the phases of Cheyne-Stokes respiration (Engel and Romano, 1944). In all the conditions in which depression of the metabolism of the central nervous system occurs as a result of deprivation of essential metabolites, continuous generalized slow waves are the rule.

A possibility is that in all cases a common focal brain-area exists which is responsible for the synchronization of the periodic cortical phenomena. Such an area would most likely be deep in some central structure in the brain. The observations of Jasper and Droogleever-Fortuyn (1947) on the origin of the spike and wave complex, indicate that stimulation of the intralaminar areas of the thalamus of the cat can result in typical alternating spikes and waves, recorded from the cortex. But the spike and wave complex only bears resemblance to the complexes here described in the repetition of wave form, the variability of which is as great in the epileptic as in the encephalitic. The periodicity of the disturbance, which is so characteristic of the records of the subacute encephalitic, is a quality only very rarely seen in the epileptic record. Discussions with Dr. Greenfield and with Professor Meyer on the sites of the main lesions in cases of subacute encephalitis, have not suggested a single structure deep in the brain which is invariably affected. Yet the lesions are so diffuse that this possibility can by no means be excluded.

Bremer and Titeca (1939) showed that the EEG of the normal cat under barbiturate narcosis develops bursts of 10–15 c/sec. activity spaced by more or less regular intervals. Similar bursts are also characteristic of the cat with the brain-stem sectioned at the foramen magnum (encéphale isolé) when the animal is asleep. Again, these writers showed similar "burst" activity as characteristic of their cats with section of the mid-brain (cerveau isolé); these animals are permanently asleep and cannot be woken. More recent work suggests that "burst" phenomena—periodic rhythmic activity separated by more or less equal intervals—develops in the cortex when sections or lesions of the brain are made at almost any level below the cortex. Lindsley, Bowden and Magoun (1949) studied the effects of acute brain-stem lesions in the anæsthetized *encéphale isolé* cat. The phenomenon of "burst" activity was again encountered when the lesions were in the mid-brain or higher. The most pronounced and prolonged effects were seen after mid-brain transection and following discrete injuries to the mid-brain tegmentum and basal diencephalon. The recurring

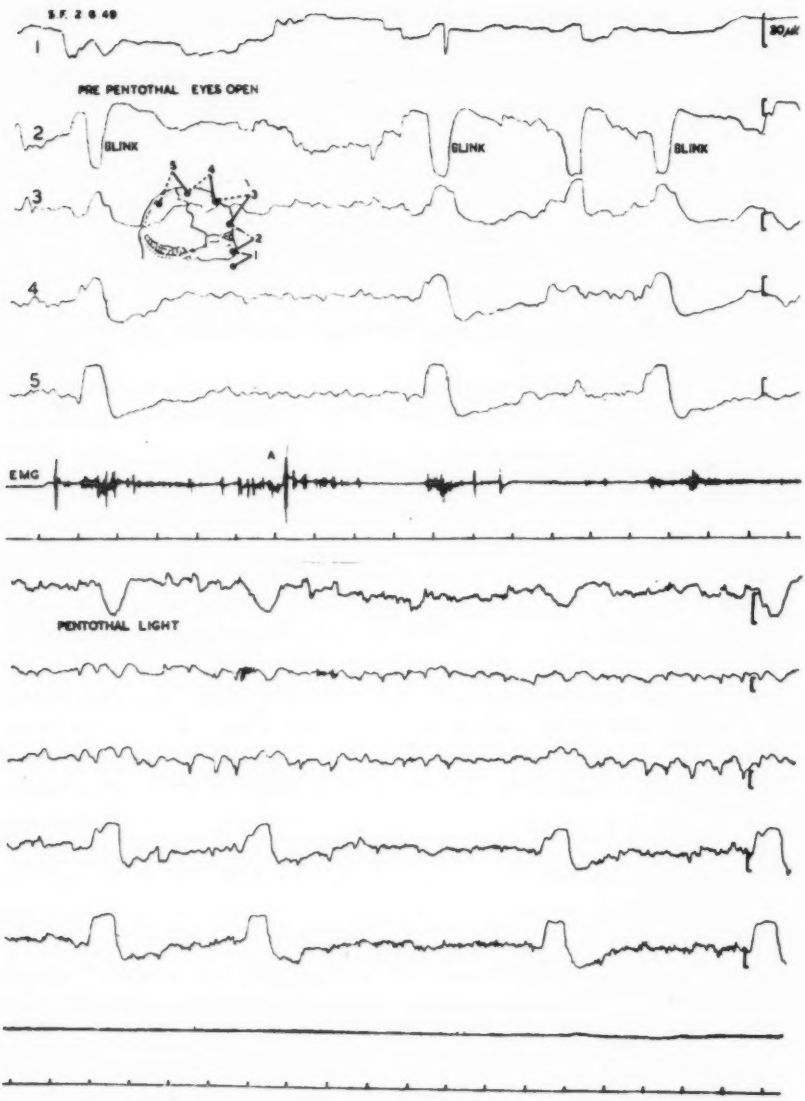

FIG. 8.—S. F. At this time each involuntary movement, recorded from the right forearm, was accompanied by a single large slow wave in the EEG (compare with the slightly greater complexity of a week earlier, fig. 3). Each movement was also associated with an eye-blink. Notice at "A" in the first record, the EMG of a voluntary movement unassociated with changes in the EEG, and about 7 seconds later a voluntary blink, which is recorded in the second and third channels only. During the second record, a few minutes later, the patient was under pentothal anæsthesia, just sufficiently deep to abolish muscle activity. The single slow waves persist, without the accompaniment of limb movements or blinks. Small recurrent spikes appeared anteriorly. (Note that in these two records the polarity of the channels is contrary to the usual practice, to which the head-diagram has inadvertently been made to conform.)

bursts of high voltage slow waves could be recorded from thalamic nuclei as well as from the cortex. The activity recorded from the thalamus was abolished by acute decortication, and conversely cortical "bursts" disappeared after acute thalamic lesions. But Kristiansen and Courtois (1949) from similar experiments in which areas of cortex were completely isolated, the white matter was sectioned and the thalamus was removed, state that different results may be obtained if an interval of some hours is allowed to elapse after the lesion is made. These workers showed that the cats electrocorticogram from a thalamectomized hemisphere developed a "regular sequence of bursts with relatively quiet intervals. Cortical undercutting gave a perfectly regular appearance of the rhythmic bursts, the intervening activity being almost completely abolished." Further, when complete subpial isolation of the same area of the cortex was performed, the patterns remain unchanged.

All the writers quoted have compared their findings with those in barbiturate narcosis and in natural sleep. This comparison is made because of the similar phenomena of "burst" activity seen both in the intact state and after lesions. However, the "bursts" encountered in the EEGs of patients suffering from subacute encephalitis differ from the "spindles" of normal human sleep by reason of the frequency of the rhythm, which is remarkedly slow in the patients here described.

The clinical accounts of these patients describe periodic involuntary movements when the illness is fully established. These are found to have a definite temporal relationship to the repetitive electrical activity (figs. 4 and 8). Since, associated with the limb movements, there are also movements of the eyes, the possibility that the potentials recorded from the scalp are due to this source has been investigated. That it can be excluded is seen in fig. 8 in which, by arrangement of electrodes across the eyes, the components due to their movement can be identified. When the subject was examined during pentothal anæsthesia, which abolished both eye and limb movements, the cortical phenomena persisted, though, in simplified form.

The observations on the post-convulsive state (fig. 7) indicate that similar phenomena to those described in these patients can occur in a human brain in the absence of structural damage. The experimental work referred to also indicates that lesions placed in the cat's brain in a wide variety of positions between the cortex and the mid-brain can likewise result in periodic activity at the cortex. It is remarkable, therefore, that this electrical pattern is not encountered more often considering the very large number of patients examined suffering from diverse lesions, and that the finding would appear to be invariable in all cases of subacute sclerosing encephalitis so far described.

SUMMARY

The electroencephalograms of 5 patients suffering from subacute progressive encephalitis are reported, and all show similar characteristics having a degree of specificity which is diagnostic of this condition. The course of the illness in fatal cases is characterized by a progressive disappearance of normal rhythms, and the appearance of episodes of high voltage slow waves which become periodic, repeating at intervals of approximately 8 seconds. When involuntary movements occur, they are associated with these episodes of slow-wave activity.

The possible relationship of the lesions in these patients to the electroencephalographic findings are discussed with reference to some recent experimental work on animals.

We desire to thank Dr. J. G. Greenfield and Professor A. Meyer for their interest and advice and Dr. Denis Leigh for contributing the case history of S. F. We are also indebted to Dr. M. R. Hess of Zurich for allowing us to mention his case, and to those physicians of the National and Maudsley Hospitals whose patients we examined.

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BASILAR IMPRESSION OF THE SKULL

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THE term Basilar Impression of the Skull is used to describe an invagination of the upper cervical spine into the posterior fossa. Associated with this invagination there is deformity of the foramen magnum with stenosis and elevation of its margins. The condition may be present without clinical evidence of neurological disturbance but in some cases there is compression of the brain-stem and upper cervical cord, disturbance of function of the lower cranial nerves, or obstruction of the cerebrospinal fluid circulation with corresponding neurological symptoms and signs. In this paper 5 cases of the condition are described in which operative treatment has been undertaken: some account is given of the development of knowledge of the subject and views on the pathogenesis are put forward.

Historical introduction.—The first description of the deformity of the skull base appears to be that of Ackermann in 1790 in a pamphlet on cretinism. He suggested that rickets was the cause of the abnormal shape of the skull and also realized that pressure on the pons and medulla might result from the deformity. Rokitansky (1844) gave a short but clear description of indentation of the skull by the cervical spine and commented that the part projecting into the cranial cavity was always thin-walled and atrophic. The cases in which he found the deformity were chronic hydrocephalics in whom the condition had apparently dated from the fœtal period.

The anthropologist Davis in 1863 described five skulls with basilar impression and it is of historical interest that three of these were found during the excavation of ancient tombs. The skull with the most marked deformity came from Llanthony Priory in Gloucestershire, and the other two from Teneriffe and Galway. Davis suggested that the "plastic deformity" of the base of the skull was due to softening of the bones and that it developed slowly and insensibly under the upward pressure of the cervical spine. Boogaard in 1865 defined the basal angle of the skull and suggested that depression of the base of the skull around the foramen magnum could be caused by any pathological condition which interfered

with the hardness of the bones at the base of the skull. He thought that hydrocephalus might be a predisposing factor in some cases but realized that basilar impression could occur without hydrocephalus.

Virchow (1876) distinguished two forms of basilar impression of the skull. He separated skulls in which the pressure of the vertebral column against the base of the skull was greater on the anterior part of the bony ring from those with greater pressure on the posterior part, and suggested that the former occurred particularly in old age and the latter in infancy. Grawitz (1880) described several skulls with basilar impression and noted that fusion of the atlas with the occipital bone or subluxation of the atlas might occur in association with it. His patients do not appear to have had neurological symptoms except one who suffered from epilepsy. He suggested that premature synostosis and syphilitic caries might cause the deformity in some cases.

The first case with definite neurological symptoms due to basilar impression was reported by Homen (1901) in Finland, who found well-marked basilar impression at post-mortem in a man of 22 who had a two years' history of diplopia, dysphagia, and a staggering gait, and who on examination had dysarthria, nystagmus, ataxia, and ankle clonus.

Schuller (1911) was the first to make the diagnosis during the lifetime of the patient by means of a lateral X-ray picture of the skull and upper cervical spine in a woman, aged 21, with occipital headache, dysarthria, dysphagia, immobility of the neck, and atrophy of the right side of the tongue.

Basilar impression was found to be fairly common in Paget's disease (Marie, Leri, and Chatelin (1912), Leri (1913), Leri and Marie (1919)). These authors stressed that the cause in Paget's disease was fixity of the foramen magnum and the structures around it with sinking of the softened base of the skull under the weight of the brain, and they mentioned that it might also occur in other conditions of softening of bone such as rickets and osteomalacia. There were no neurological symptoms and signs in their cases and the French workers suggested that raised intracranial pressure did not occur as the cranial cavity gained in its transverse diameter in Paget's disease as the vertical diameter was diminished.

Ebenius (1934) in Stockholm described 4 patients with neurological disturbance due to basilar impression; in 2 of them the skull deformity was probably due to the bone softening of rickets. The important point about his paper is the first description of operative treatment. In 2 patients suboccipital decompression with removal of the arch of the atlas was carried out and in both there was symptomatic improvement.

There were scattered case-reports in the literature of the nineteen-

twenties and thirties; Mme Dejerine (1926), Fiszhout and Jabokrzycki (1938), Bau-Prussack and Fiszhout-Zeldowicz (1938), Alessi (1939), but attention was focused on the condition by Chamberlain's paper in 1939. He described 4 cases, of which 3 had neurological disturbance. In 2 of these patients suboccipital craniotomy and laminectomy of the upper three cervical vertebræ was performed. One made a complete recovery from a spastic tetraparesis, while the second improved for a few months and his condition then deteriorated. The importance of this paper lies in the description of the radiological appearances of basilar impression, particularly the description of what has come to be known as Chamberlain's line. In a true lateral picture of the skull and cervical spine this is a line drawn from the back of the hard palate to the posterior border of the foramen magnum, and normally it lies above all parts of the atlas and axis (fig. 1)[1]. If basilar impression is present part of the odontoid process and in advanced cases other parts of the axis and of the atlas are above this line. This radiological sign is of considerable help in the diagnosis of basilar impression.

After the publication of Chamberlain's paper the condition attracted considerable attention, particularly in the United States, and a number of other publications have appeared; Oldberg and Gustafson (1940), Laube and Turner (1940–41), List (1941), Dereymaeker (1941), Furst and Ostrum (1942), Craig, Walsh, and Camp (1942), Curtis and Verbrugghen (1944), Hadley (1944), Little and Pascucci (1945). Comparatively little attention has been given to it in the United Kingdom, only 2 single case reports have been published: de Vet (1940) describing a very advanced case from Holland, and Mayersky (1949) a case from Hungary.

Nomenclature

The term Platybasia is sometimes used to describe the deformity of the base of the skull which we are calling basilar impression. Platybasia is used by anthropologists to denote a flattening of the base of the skull with an increase of the basal angle to more than 150° (fig. 1, Plate XX, *facing* p. 426), a condition which can occur without actual invagination and deformity of the foramen magnum, and for the condition under consideration the terms basilar impression or basilar invagination are more satisfactory.

Clinical Course

The age, sex, and duration of symptoms in our 5 cases are shown in Table I.

[1] Except the two line drawings (figs. 2 and 4) and fig. 3, which are in the text, all the figures are to be found on plates at the end of the Paper.

TABLE I

Case	1	2	3	4	5
Sex	F	M	M	M	F
Age	23	17	22	40	27
Duration of symptoms	8 months	2 years	probably all his life	8-10 yrs.	6 yrs.

In only one case could symptoms be said to date from birth; the patient was known to have been born with hydrocephalus, while other symptoms due to basilar impression appeared at the age of 12 and gradually became more disabling after he was 19.

EFFECT OF TRAUMA ON THE APPEARANCE OF SYMPTOMS

In 2 cases injury to the head appeared to precipitate the symptoms. In Case 2 the initial headaches started immediately after a fall backwards down a garage pit, and Case 3, who had hydrocephalus and dysarthria before the injury, developed double vision following a fall on to his face.

SYMPTOMS

The onset of symptoms is insidious and these are usually slowly progressive. In 2 patients only was there a temporary improvement following a period of rest in bed.

There are four main types of neurological picture in basilar impression, but in the majority of cases combinations of these types occur. They are:

(1) Hydrocephalus and raised intracranial pressure.

(2) Bilateral cerebellar disturbance.

(3) Interference with the function of the lower cranial nerves.

(4) Spinal cord compression at the level of the foramen magnum.

Table II indicates the major presenting symptoms in the cases of this series.

TABLE II

Cervical pain	5 cases
Headache	4 cases
Cranial nerve symptoms	3 cases
Unsteadiness of gait	4 cases
Weakness or numbness of limbs	1 case

Cervical pain is an important symptom and may occur without generalized headache. 3 patients described it as a constant pain at the back of the neck and base of the skull; in one of them it was increased by coughing, while in a fourth patient severe cervical and suboccipital pain came on whenever she coughed or sneezed.

Headache tends to be frontal and may also be precipitated by coughing and straining. In Case 1 where there was raised intracranial pressure the headache became generalized and was accompanied by vomiting.

Physical Signs

Table III indicates the type of physical signs in our cases.

Table III

Physical deformity	5 cases
Papilloedema	1 case
Cranial nerve involvement	4 cases
Cerebellar disturbance	4 cases
Pyramidal tract involvement	5 cases
Sensory changes—cutaneous	1 case
—posterior columns	3 cases
Respiratory disorder	4 cases

Physical Deformity

The most characteristic abnormality is shortness of the neck with the external occipital protuberance approaching the vertebra prominens. In de Vet's (1940) case only one finger could be inserted between these structures and the head appeared almost to rest on the shoulders. In none of our cases was the deformity as severe as this but in one case the marked shortening of the neck made the clinical diagnosis possible and in three others there was shortening of slighter degree. Passive movements of the neck may be restricted and painful. In 2 patients there was enlargement of the head, in one of considerable degree due to long-standing hydrocephalus, and in this boy there was infantilism of similar causation. In 2 cases there was an upper dorsal scoliosis.

Cranial nerve involvement is common and any of the nerves in the posterior fossa may be affected. In Case 1, who had raised intracranial pressure in addition, there was paresis of the right sixth and seventh nerves, left-sided deafness, and bilateral fibrillation of the tongue; in Case 2 there was a right facial and palatal palsy and absent corneal reflexes; in Case 3 a right-sided palatal, pharyngeal, and laryngeal palsy; and in Case 4 bilateral trigeminal sensory impairment. In Case 5 there was no cranial nerve dysfunction.

Cerebellar disturbance was evident in 4 cases, the principal symptom being unsteadiness in walking of cerebellar type. In 2 patients there was inco-ordination in the arms as well.

Nystagmus was present in 4 patients on lateral and upward movements of the eyes and in 3 of them there was a marked rotatory element in the nystagmus.

Pyramidal tract involvement.—Reflex signs of pyramidal tract disturbance were present in all 5 cases but weakness, as distinct from inco-ordination and sensory disturbance, was not a prominent feature.

Sensory disturbance.—Cutaneous sensory disturbance was found in only one case, in whom there was slight impairment of all modalities on the right side from C.2 to D.8 segments. Other authors have described sensory impairment of the type found in syringomyelia of the cervical cord but this has not occurred in our cases.

Impairment of posterior column sensation has been a commoner finding; in 2 patients there was gross loss of appreciation of position and vibration in the legs, and in one of them similar impairment together with astereognosis in the hands. In another patient there was slight impairment of position sense in the right hand and foot.

Disturbance of respiratory rate was noted in 3 patients and this has also been recorded by Craig, Walsh, and Camp (1942). In the most obvious case the respiratory rate dropped at times to 7–8 per minute. This occurred particularly when the patient was lying down and the rate returned to normal when he sat up. The bradypnœa was not necessarily associated with internal hydrocephalus or a foraminal pressure cone, and is probably due to embarrassment of the respiratory centres in the brain-stem by the bony deformity. It disappeared after operation, in one case dramatically as the medullary compression was relieved.

Lumbar puncture was performed in only 2 of our patients and in them there was a normal response in the Queckenstedt test and the cell and protein content of the C.S.F. was normal.

Diagnosis

Basilar impression of the skull causing neurological symptoms is not an excessively rare condition and it is probable that some cases remain undiagnosed, being considered to be examples of disseminated sclerosis, syringomyelia, brain-stem syndromes of uncertain causation, or posterior fossa tumours. At times it may be possible to make the diagnosis clinically by finding an abnormally short neck, possibly with restricted cervical movements, in association with neurological signs of a high cervical cord or brain-stem lesion. More frequently the physical deformity is slight and it is our opinion that in all cases with neurological evidence of a high cervical cord or brain-stem lesion or symptoms suggestive of a posterior fossa tumour, lateral X-rays of the skull and upper cervical spine should be taken together with a half-axial view of the skull to demonstrate the shape and position of the foramen magnum, with the possibility of basilar impression in mind.

Early diagnosis is important as operative treatment should be undertaken as early as possible after neurological symptoms and signs have developed.

Radiological Appearances

It seems likely that an awareness of the radiological features of the condition would lead to its more frequent recognition. The essential change on skull films is an elevation to a greater or lesser extent of the anterior arch of the atlas and tip of the odontoid process above Chamberlain's line in lateral projections. In basal projections stenosis of the foramen magnum may be seen and also irregularity and asymmetry of the petrous portions of the temporal bones. Changes indicative of a long-standing hydrocephalus may be added (convolutional atrophy, spreading of the cranial sutures, and the form of erosion of the clinoid processes typical of third ventricular enlargement). Tomograms may be of value in revealing details of the region of the foramen magnum which are hidden in the plain films, particularly in indicating the extent of the deformity, and demonstrating that the tip of the odontoid process has perhaps risen to the level of the posterior clinoid processes.

Pneumography, while it provides no direct diagnostic assistance, may be helpful in indicating the presence and degree of internal hydrocephalus. It was performed in 3 of the patients in this series and in 2 there was dilatation of the ventricular system (extreme in 1 case), while in another with severe bony deformity the ventricular system was of normal dimensions.

Operative Findings and Results

The operative procedure is essentially a suboccipital craniectomy with removal of the arch of the atlas followed by a wide opening of the dura mater to provide a decompression. Since these patients may show evidence of brain-stem or high cervical cord compression with in particular respiratory embarrassment, it has been found of great assistance to operate with the patient in the sitting position or its equivalent.

The operative findings are described in the individual case records and will be but briefly summarized here. In every case a well-marked cranial invagination of the occipital bone was present. This was more obvious on the anterior and lateral aspect of the foramen magnum than posterior to it. The foramen magnum was stenosed in all but one case (Case 5), and in every case its margin was turned upwards into the posterior fossa, and this in turning was carried on to the posterior portion of the margin. In every case the posterior arch of the atlas was pressed firmly against the occipital bone and was in addition to some extent covered by the posteriorly placed uninvaginated portion of the occipital bone. At the level of the foramen magnum there appeared in all cases to be a slight narrowing of the dural theca and when this stricture was divided the normal respiratory rhythm was restored, dramatically in one

patient (Case 2). In all cases (except Case 4) there was present a tonsillar herniation through the foramen magnum. This was usually of the type associated with a rise in pressure in the posterior cranial fossa but in one case (Case 5) the portions of the cerebellum lying in the spinal canal were thin and leaf-like. There was nothing else in the appearances in this case to suggest an Arnold Chiari malformation. In 3 patients there was definite flattening of the medulla at the level of the foramen magnum; in one patient (Case 4) this was extreme, the nervous tissue being reduced to a flat band. In only one patient in the series (Case 4) was the abnormal course of the uppermost cervical posterior root (described in detail in the discussion of the ætiology of the deformity) noted. It is possible that in the earlier cases it was overlooked, and the tonsillar herniations in these and in the latest case rendered exploration of the upper spinal canal incomplete. However, in a case not included in the present series an exactly similar abnormality of the posterior nerve root with flattening of the spinal cord was present. This case was excluded from the series since there was a cystic intramedullary lesion in the upper cervical segments. Though this might have been secondary to stenosis of the foramen magnum the absence of definite basilar impression suggested that the case did not merit inclusion in the series.

The results of the surgical treatment of basilar impression are considerably influenced by the length of the time interval between the onset of symptoms, due to the deformity, and their attempted relief by surgery. When a gross internal hydrocephalus has developed and there is marked evidence of compression of the medulla or cervical cord, the risks of operation are increased, and while symptoms may be relieved the prospects of a complete restoration of function are remote. On the other hand when operation is performed at an early stage the development of severe disability is prevented and the patient restored to full health. The first patient died of pulmonary complications shortly after the second operation in a two-stage procedure. She was so seriously ill that the risk of any operation was very great. In the second case recovery has been such that the patient has returned to heavy work as a farm labourer and his only residual abnormality is a unilateral palatal weakness. The most recently treated case (Case 5) has made good progress and it is hoped that a complete or nearly complete recovery will occur. In Cases 3 and 4 the condition was of long standing with an enormous hydrocephalus in Case 3 and gross injury to the spinal cord in Case 4. In neither case could good restoration of function be expected but cervical and head pain have been relieved and respiratory embarrassment overcome. Both patients are doing light manual work. From our experience with these patients we feel that surgery can do much for them and that with earlier diagnosis and treat-

ment the severe disability which may arise from long-standing deformity could be prevented.

Ætiology of Basilar Impression and the Associated Neurological Disturbances

Cases of basilar impression fall into two ætiological groups; in one, which may be called the secondary group, the deformity is due to a skeletal disease which causes softening of the skull base. Here the weight of the head and the loss of rigidity of the weight transmitting area around the occipital condyles cause the skull to sink downwards around the condyles and the cervical spine. Secondary basilar impression occurs fairly frequently in advanced Paget's disease but usually there is no clinical neurological disturbance in these cases. Ray (1942) and Wycis (1945) have, however, described neurological symptoms in Paget's disease from this cause and in both cases the symptoms were relieved by suboccipital craniotomy and high cervical laminectomy. In our first patient the diagnosis of osteogenesis imperfecta had been made early in her life and the structural abnormality of the cranium probably led to the gross deformity of the skull which she exhibited when examined by us. Since no skull films were made in early life it is not possible to do more than point to the probable association between the skeletal abnormality of early life and the subsequent cranial deformity. One of Ray's patients also suffered from osteogenesis imperfecta. In 2 of Ebenius's cases and in Mayersky's patient softening of bone due to rickets was considered to be the cause of the basilar impression. Osteomalacia and hyperparathyroidism have also been thought to be possible causes as a result of generalized softening of bone.

In another and larger group of cases, classed as primary, no skeletal disease which could account for the development of the deformity has been demonstrated. It is generally accepted that here it is a congenital developmental anomaly. This view has been accepted by most writers on the subject (e.g. Gustafson and Oldberg, 1940; List, 1941; Craig, Walsh and Camp, 1942), and it has been pointed out that basilar impression is not infrequently associated with such other skeletal deformities as occipitalization of the atlas, Klippel-Feil deformity or spina bifida. Consideration of the 4 cases in the present series in which the deformity appears to be of the primary type provides no evidence to suggest that it should be regarded as a congenital developmental one. Thus in no case was there an associated spina bifida and none showed occipitalization of the atlas. Neither did any of the cases show the Klippel-Feil deformity, though in Case 4 an abnormality of the second and third cervical vertebræ was present. This suggested the possibility that the deformity might be due to mechanical factors alone in the presence of a structural weakness of the

weight-transmitting area of the skull base. The features of the deformity which require explanation are (1) the impression of the region of the foramen magnum into the skull, (2) the stenosis of the foramen magnum with the elevation of its margin, (3) in Case 4 the upward course of the most cephalad cervical posterior nerve root—and this root alone.

Certain anatomical features of the skull base and atlas are illustrated in fig. 2. The occipital condyles are situated on each side of the fora-

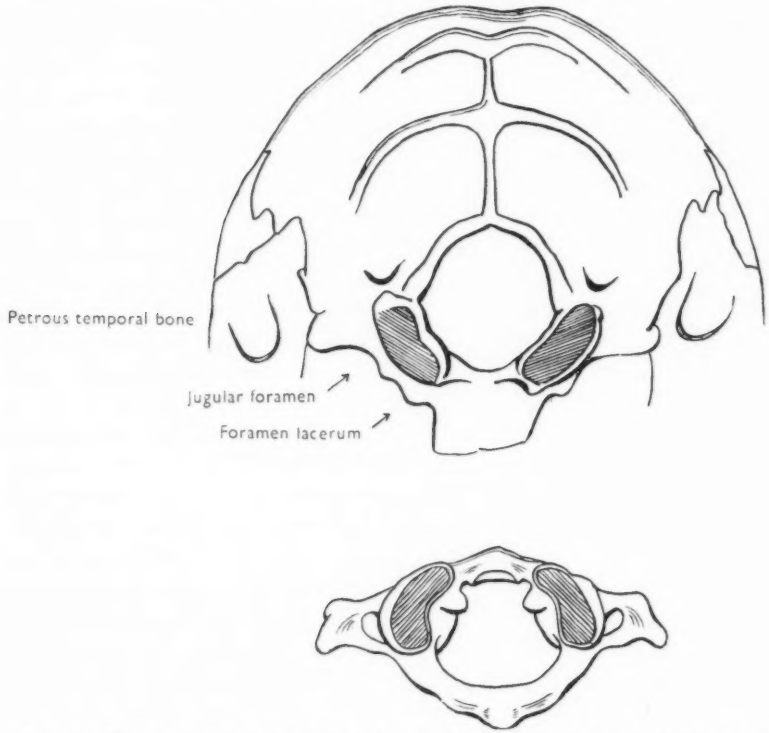

FIG. 2.—The anatomy of the occipital condyles and superior articular facets of the atlas.

men magnum and entirely anterior to its equator. They are obliquely placed, their long axes being directed forwards and inwards and the articular surfaces inclined laterally as well as inferiorly so that they are grasped between the upper articular facets of the atlas which have a medial inclination. It would also appear that the posterior portion of the occipital condyles possess a rigid lateral support in the articulation of the jugular process of the occipital bone with the petrous portion of the temporal bone. Anteriorly the condyle lacks such support being separated

from the temporal bone by the jugular and middle lacerate foramina, while in the mid-line the basiocciput is united to the basisphenoid by a cartilaginous plate until the 20th year of life.

Assuming the presence of a structural weakness—congenital or acquired—in the bone or cartilage in the region under consideration it is believed that all the features of the deformity seen in our cases are

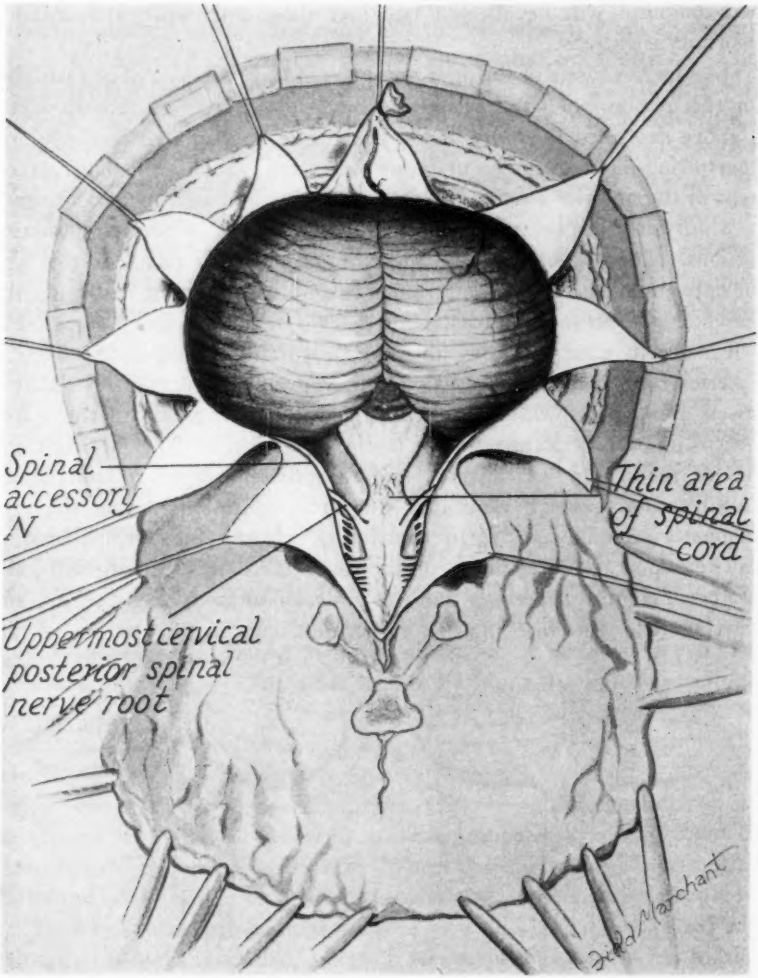

FIG. 3.—Sketch of operative findings in Case 3. The thinning of the upper cervical spinal cord and upward inclination of the first cervical posterior nerve root are shown.

explicable. The position and the relative lack of support of the anterior portions of the occipital condyles ensures that when the skull base gives way under the weight of the head and is impressed into the cranium it is the anterior margin of the foramen magnum and the basiocciput which are most affected. The anterior arch of the atlas and the tip of the odontoid process may then come into contact with the basiocciput and subject this region to additional stress. The posterior portion of the foramen magnum will be affected late and then only when the anterior deformity is extreme.

The superior facets of the atlas are directed medially as well as cranially. For this reason when the occipital condyles are impressed into the skull as above described they will at the same time be displaced medially and a narrowing of the foramen magnum will occur. Such a medial displacement of the anterior portions of the condyles might be expected to result in a forward displacement of their more widely separated posterior portions. These would then be approximated in their turn. In this way not only could stenosis of the foramen magnum be brought about but the characteristic turning upwards of the margin of the foramen is explicable.

Finally in Case 4 it was noted (fig. 3) that the uppermost cervical posterior root—and that root alone—had an abnormal course in that it passed obliquely upwards between its central attachments to the spinal cord to its peripheral attachment to the dural theca. The fact that one pair of roots only was affected and that there was no Arnold Chiari malformation makes it clear that the abnormality was not of the type frequently seen in cases of myelomeningocœle. A possible explanation depends upon the attachment of the dural theca to the margins of the foramen magnum superiorly and the posterior surfaces of the second and third cervical vertebræ (fig. 4). The elevation of the margin of the

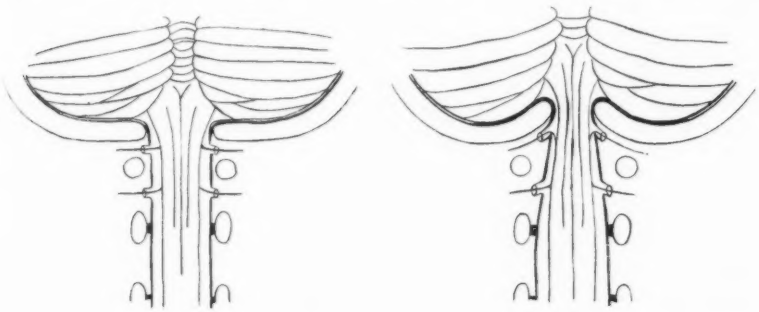

FIG. 4.—Diagrammatic drawings to indicate how the normal course of the uppermost cervical posterior nerve root (A) may be altered by the invagination of the margins of the foramen magnum (B).

foramen magnum would lead to a dragging upwards of the dural theca, but the attachment of the latter to the bodies of the second and third cervical vertebræ would limit the displacement to the extreme upper end of the theca. The dural sheath of the uppermost cervical nerve would be elevated by the displacement and in this way the abnormal course of its posterior root may possibly be explained.

It will be seen that the characteristic deformity of the foramen magnum in cases of basilar impression can be understood from a study of the architecture of the region of the occipito-atlantoid joints. The unexplained feature is the factor which causes the skull base to give way. No light can be thrown on this but it is possible that different types of congenial or acquired structural abnormality in bone or cartilage could be responsible and in this respect the condition may be likened to coxa vara.

Turning to the ætiology of neurological disturbance in cases of basilar impression, it has been generally accepted that it is the result of compression of the contents of the posterior fossa by the bony deformity. It should, however, be mentioned that some have suggested (e.g. List) that symptoms and signs of involvement of the nervous system may depend on a developmental abnormality in its tissue at the level of the overlying congenital abnormality of skull and spine. The nervous disturbance is thus regarded as analogous with that occurring in the presence of a myelomeningocœle associated with a spina bifida. However, in our cases there is less reason for regarding the nervous lesions as developmental errors than there is for supposing that the bony deformity is a congenital one. Those who accept the view that the deformity is a congenital one have been puzzled to explain why the neurological disturbance should perhaps not appear for many years. Chamberlain suggests that the nervous tissue in early life may be capable of tolerating traumata which cannot be borne later in life. He also quotes a suggestion made to him by Light that symptoms might be produced in adolescence when growth of the spine occurs after the spinal cord has attained its adult length. However, if one assumes that the deformity is a progressive post-natal one the time of onset of neurological disturbance will depend on the rapidity of development of this deformity. Perhaps the two main clinical groups may depend upon the variations in the type of deformity. Where there is great elevation of the clivus and severe reduction in the volume of the posterior fossa the picture will be one of raised intracranial pressure such as might be associated with a posterior fossa neoplasm; where the elevation of the clivus is less marked but stenosis of the foramen magnum is severe, the picture will be one of a high cervical cord or medullary compression.

Relationship to Syringomyelia

Signs indicative of syringomyelia have not occurred in our cases. Other authors have described cases of basilar impression with sensory changes highly suggestive of syringomyelia affecting the upper cervical cord, and in two of Gustafson and Oldberg's (1940) cases syringomyelic cavitation was demonstrated. In the first of these a laminectomy of C.4–6 revealed a cystic condition of the cord, and some years later the diagnosis of basilar impression was made. In the other case post-mortem examination showed a syringomyelic cavity extending from C.4 segment to the lower end of the cord together with marked basilar impression causing constriction of the cord.

It is possible that a primary syringomyelia may be present in some cases, but this may not be the only reason for intramedullary cavitation in association with basilar impression. Lichtenstein (1943) has suggested that secondary syringomyelic changes can occur from the interference with the blood supply of the cord which follows compression of the spinal arteries and veins. Thomas and Hauser (1904) thought that cavitation in the cord could be produced by vascular disease; Klotz (1913) demonstrated intramedullary cavitation following a spinal thrombosis, and one of us (Turner, 1948) has described a case of post-meningitic spinal arachnoiditis with well-marked cavitation in the cord resulting in all probability from interference with the blood supply.

The presence of intramedullary changes of this type, whether due to a true syringomyelia or due to secondary changes of vascular origin, may explain the persistence of symptoms and signs in some cases following operation.

Summary

(1) Five cases of basilar impression of the skull in which operative treatment was carried out are described.

(2) Basilar impression may cause hydrocephalus and raised intracranial pressure, bilateral cerebellar disturbance, interference with the function of the lower cranial nerves or spinal cord compression at the level of the foramen magnum, and in some cases combinations of these disturbances are present.

(3) Clinical diagnosis may be possible when the neck is abnormally short but the diagnosis can usually only be made with certainty by radiological examination, the most important feature being the demonstration of part of the cervical spine rising above Chamberlain's line.

(4) Views on the pathogenesis of basilar impression are put forward. It appears to occur gradually when there is a congenital or acquired structural weakness of the weight-bearing area of the skull base.

(5) Suboccipital craniectomy and removal of the arch of the atlas with wide opening of the dura may result in considerable relief of symptoms, especially if operation is performed before there is gross internal hydrocephalus or severe damage to the brain-stem and upper cervical cord.

Part of this paper was given by one of us (J. E. A. O'C.) at a Meeting of the Society of British Neurological Surgeons in November 1948. This author would also wish to record his indebtedness to Mr. G. Dower, his house-surgeon at that time. Several of the sketches published in this paper were made by him.

Case Histories

Case 1.—*Summary.* Osteogenesis imperfecta. Raised intracranial pressure. Radiological demonstration of basilar impression. Two-stage operation. Death due to pulmonary infection. R. C., a woman aged 23, was admitted to St. Bartholomew's Hospital on March 10, 1944. She had previously been in the hospital at the age of 12 on account of pain in the back. She then gave a history of having fractured her left leg at the age of 7 weeks and her right ilium at 5 years. After X-ray examination a diagnosis of osteogenesis imperfecta had been made. The pain in the back had gradually become less and she had remained well until eight months before her readmission, when she began to have pain at the back of the neck which gradually became more severe and was relieved to some extent by lying down. Shortly after this she began to have a feeling of pins and needles in the face which was precipitated by sudden movements of the body, and for five weeks before admission she had increasingly severe headaches and for two weeks repeated attacks of vomiting. There had been left-sided deafness for twelve months and bilateral tinnitus for eight months, but no vertigo.

On examination she was of small stature with a large head and well-marked prognathism. The neck was short and the head sunken between the shoulders. Flexion and extension of the neck were relatively free but rotation was grossly limited.

On neurological examination there was severe bilateral papillœdema with hæmorrhages and exudate. There was no nystagmus but a right external rectus palsy and lower motor neurone weakness of the right side of the face were found. There was diminished hearing in the left ear and marked bilateral fibrillation of the tongue.

Posture was poorly maintained in both arms but there was no definite weakness or inco-ordination. Tendon-jerks were brisker on the right than the left, abdominal reflexes were brisker on the left, and both plantar responses were extensor. There was no definite sensory impairment except for a suggestion of impaired position sense in all four limbs.

The EEG record was very abnormal. There was an irregular 10 c/sec. alpha rhythm, better developed and of larger voltage on the right, with many very large voltage slow waves superimposed on this. There were many paroxysmal outbursts of 3–6 c/sec. waves arising from the central leads especially on the left, and a focus of slower waves on the left fronto-temporal region.

Radiological examination of the skull revealed gross basilar impression with marked stenosis of the foramen magnum. In addition there were changes suggesting the presence of an internal hydrocephalus of long-standing, expansion and thinning of the calvarium with erosion of the clinoid processes (figs. 5, 6 and 7). Tomography revealed that the odontoid process had risen almost to the level of the dorsum sellæ. Examination of several long bones suggested that they were hypoplastic with poor cortical development.

Ventriculography revealed a very large internal hydrocephalus (fig 8). The posterior portion of the third ventricle was not filled, a finding which was regarded as being due to the herniation upwards through the tentorial opening of some of the contents of the small posterior cranial fossa (reversed tentorial pressure cone).

A diagnosis of secondary basilar impression was made and operation decided upon in view of the rapid deterioration in the patient's condition. At a first-stage procedure on 18.3.44 a removal of the basiocciput and arch of the atlas on the right and the establishment of ventricular drainage alone was possible. At a second-stage operation six days later the remainder of the impressed occipital bone was excised and the left half of the arch of the atlas and the spine and lamina of the axis were excised with wide opening of the dura.

Post-operatively evidence of a severe pulmonary infection appeared with death on the third post-operative day. At autopsy the local condition was satisfactory with no evidence of infection. There were widespread pyæmic abscesses in all the viscera.

Case 2.—*Summary.* Headaches and pain at the back of the neck followed by brain-stem involvement. Radiological demonstration of basilar impression. Sub-occipital craniectomy, removal of the arch of the atlas, and opening of the dura. Complete relief of symptoms.

T. R., a male aged 17, was admitted to St. Bartholomew's Hospital on February 16, 1945. Two years earlier he had fallen backwards down a garage pit and struck the back of his head without losing consciousness. Headaches commenced a few days later, these were on the right side of the forehead at first but for twelve months he had been having almost continuous pain at the back of the neck and in the occipital region. For six months his walking had become unsteady and during the same period there had been nasal regurgitation of fluids and his voice had developed a nasal quality. These symptoms had gradually become worse.

On examination.—He was noted to hold his forehead when he coughed. His head was held flexed to the left and at times the occiput was rotated to this side. The neck was also perhaps a little short and its movements were restricted and painful. The fundi showed very deep optic cups but were otherwise normal. There was horizontal nystagmus on lateral movements of the eyes, and the corneal reflexes were both diminished. The palate moved poorly and deviated markedly to the left on phonation. There was slight weakness of the right arm and its posture was poorly maintained. Tone in the right arm and leg was diminished and there was a little ataxia of the right arm in the finger to nose test. The reflexes were normal except that the right knee-jerk was brisker than the left, and the abdominal reflexes were absent. There was no sensory impairment. When he walked he staggered to either side.

An EEG showed slight dysrhythmia but no other abnormality. Radiographic examination of the skull showed a moderate degree of basilar impression: in addition asymmetry of the anterior wall of the posterior fossa was demonstrated figs. 9 and 10). Ventriculography revealed a slight dilatation of the whole ventricular system.

The significance of the relatively minor radiological changes was not understood at this time, and the provisional diagnosis of a pontine tumour was made. An attempt to explore the posterior fossa had to be abandoned before the operation commenced because of persistent apnœa when the patient was placed in the prone position. Following a transient improvement which permitted his return home his condition deteriorated and he was readmitted on 31.5.45 so that a further attempt at exploration might be made.

On examination on his readmission the nasal speech had become more marked and at times it was difficult to understand what he said. Both corneal reflexes were now absent and there was a right lower facial paresis. The palate moved very poorly and deviated to the left. Tone was diminished in the right arm and leg

and the jerks were very brisk, the right knee-jerk being brisker than the left, the abdominal reflexes were absent, and the plantar responses were flexor. There was slight impairment of position sense in the right hand and foot, and his gait was very ataxic.

On 16.6.45 a suboccipital exploration was carried out and when the muscles had been reflected it was clear that there was a well-marked bony deformity involving the skull base and cervical spine. The region of the foramen magnum was invaginated into the cranium and the posterior arch of the atlas was pressed tightly against the skull and partly covered by the uninvaginated portion of the occipital bone. A wide suboccipital removal of bone was done and the posterior arch of the atlas excised. The dura mater was widely opened and there was an immediate increase in respiration rate, from 8 to 17 per minute. A well-marked tonsillar herniation was present but there was no evidence of neoplasm in the posterior cranial fossa.

When discharged from hospital the patient was well, having lost his headache, ataxic gait, and difficulty in swallowing fluids. When last examined three and a half years after operation he was in good health and employed as an agricultural labourer. On examination the decompression was concave and the only abnormal sign was a possible slight weakness of the right side of the palate.

Case 3.—Summary. Congenital hydrocephalus with infantilism. Later development of brain-stem involvement. Clinical and radiological diagnosis of basilar impression with hydrocephalus. Suboccipital craniectomy, removal of the arch of the atlas, and opening of the dura. Convalescence complicated by bronchopneumonia and obstruction of C.S.F. circulation. Considerable post-operative relief of bulbar symptoms.

E. K., a male aged 22, was admitted to St. Bartholomew's Hospital on October 30, 1946. He was born with hydrocephalus and was said to have had occasional fits during his early childhood but none since then. In early life he had difficulty in micturition, for which he was in hospital; he had occasional attacks of bronchitis, and had had treatment for a "congenital scoliosis." His voice had always been of a nasal quality.

Ten years previously he had tripped and fallen on his face, and following this he developed double vision which had persisted. Five years previously he noted some unsteadiness when he walked and for three years he had been having frequent vertical headaches. For about the same time he had had occasional attacks which started with "a sick feeling in the stomach which spread upwards, making his lower jaw tremble"; this would last for about twenty minutes.

For two years he had had nasal regurgitation of fluids, difficulty in swallowing, and a sensation of being strangled, and these symptoms had become progressively worse. Frequently he woke at night with severe choking attacks. He was able to do light work as a cleaner.

On examination his appearance was infantile and there was deficient growth of hair on the trunk (figs. 11 and 12). The skull was hydrocephalic with a circumference of 24 in., and the neck was short. The fundi showed myelinated nerve fibres but no other abnormality. There was weakness of the left external rectus and a coarse rotatory nystagmus on lateral movements of the eyes. Slight weakness of the masticatory muscles on the right was found together with reduction of the right corneal reflex and reduced sensibility in the distribution of the right trigeminal nerve. There was paralysis of the right side of the palate and pharynx and the right vocal cord was immobile. The palatal and pharyngeal reflexes were absent on the right. There was no wasting or weakness of the tongue.

In the limbs there was no wasting or weakness and no sensory impairment. Co-ordination was normal in the arms but he walked on a wide base with some ataxia. Tendon-jerks were abnormally brisk, the abdominal reflexes were absent.

the plantar responses were extensor. There was a mid-dorsal kyphoscoliosis and slight bilateral pes cavus.

Radiological examination of the skull showed the changes of long-standing hydrocephalus and well-marked basilar impression with deformation of the foramen magnum (fig. 13). Blood W.R. was negative.

A diagnosis of infantile hydrocephalus and basilar impression was made. Although it was clear that operative treatment of the latter deformity would not be without risk and that it would alleviate but a proportion of his symptoms, operation was carried out on 6.11.46 with the patient in the sitting position, and a suboccipital decompression performed with removal of the posterior arch of the atlas and wide opening of the dura mater. There was a displacement of the occipital sinus to the right of the mid-line. The region of the foramen magnum was impressed to a marked degree and the margin of the foramen grossly incurved so that it was placed at a considerable higher level than was the surrounding impressed bone. There was a well-marked foraminal pressure cone.

Post-operatively the patient's convalescence was stormy. On the day after operation he developed evidence of bronchopneumonia and remained critically ill for several days. Later the decompression became full and tense and repeated lumbar puncture was required over a period of eight weeks. The normal cerebrospinal fluid circulation then appeared to be restored so that although the decompression remained full it was no longer tense. Five weeks post-operatively the patient commenced to have repeated pyrexial attacks which continued over a period of a month: the explanation of these was not discovered.

On discharge from hospital almost eleven weeks after operation his condition had improved. He has lost his headache, no longer suffered from choking sensations, and was swallowing with greater ease. When last seen two and a half years post-operatively he had improved further. There was no headache or sickness and there had been no recurrence of the strangling sensation. He also had been able to work more easily and was employed as a cabinet maker. The decompression remained full but it was soft. The nystagmus and palatal palsy were unchanged.

Case 4.—*Summary.* History of compression of the spinal cord at the level of the foramen magnum associated with an abnormally short neck. Clinical and radiological diagnosis of basilar impression. Suboccipital craniectomy, removal of arch of atlas and fused second and third cervical spines, and opening of the dura. Post-operative relief of headache and bradypnœa but only slight improvement in other symptoms.

E. C., a male aged 40, was admitted to St. Bartholomew's Hospital on April 18, 1948. For about ten years he had noted some stiffness and numbness of the right shoulder and numbness of the right hand and forearm; this had persisted but caused little disability. For five years his gait had been unsteady, he did not seem to have proper control of his legs, and this unsteadiness had gradually become worse and on occasions he fell on account of it. For four years he had had attacks of pain in the left iliac fossa which came on particularly when he stood for long or when he walked. The pain was not related to the taking of food and there were no other abdominal symptoms. Six months before admission the numbness in the right arm had become more marked and at times there was tremor of the right arm.

Two months before admission he began to have headaches; these started in the forehead and spread to the back of the neck. In the previous two to three weeks he had occasional attacks of vertigo in which his surroundings seemed to rotate round him, but he had not fallen down in these attacks.

In his past history he had a head injury when aged 15 and was unconscious for some days, but further details of this injury could not be obtained.

On examination his neck was unusally short and the head was held tilted to

the right. Rotation of the neck was restricted and caused pain. There was a slight upper dorsal scoliosis with convexity to the right.

Fundi were normal, there was no ocular paresis but there was a coarse rotatory nystagmus on lateral movement of the eyes, and on looking upwards there was a more rapid rotatory nystagmus. Corneal reflexes were present but there was some impairment of pin-prick sensation but not of sensation to light touch over the trigeminal distribution on both sides. There was bilateral chronic otitis media with perforation of the drums.

In the arms there was no wasting but there was slight weakness of the right wrist and fingers as compared with the left. There was bilateral intention tremor and considerable inco-ordination of rapid movements. There was increase of extensor tone in both legs with slight general weakness of the left leg, and his gait was broad-based with considerable ataxia. Romberg's sign was positive. All the tendon-jerks were abnormally brisk, particularly on the left, the abdominal reflexes were sluggish, and the plantar responses were extensor.

Sensory testing indicated impairment of all forms of cutaneous sensation on the right side from C.2 to D.8 segments but there was no complete loss of cutaneous sensibility. Sense of position was severely impaired in the fingers and toes on both sides, stereognosis was poor in the hands, especially the right. Appreciation of vibration was impaired in the arms and more severely so in the legs, but it was not completely absent.

While he was in hospital it was noted that his respiration frequently dropped to eight per minute and breathing became irregular at times, particularly when he was asleep.

Lumbar puncture which was performed at another hospital gave an initial pressure of 170 mm.; there was a free rise on bilateral jugular compression. C.S.F. contained 5 cells per c.mm., protein content was 40 mg. per cent, Lange curve showed no change, and the W.R. was negative in both blood and C.S.F.

Radiological examination of the skull showed a well-marked basilar impression (figs. 14 and 15). Fusion of the second and third cervical vertebral bodies was present. Ventriculography revealed no abnormality.

A diagnosis of basilar impression was made and operation decided upon. With the patient in the sitting position, the basiocciput and upper cervical spines were exposed. There was a well-marked invagination of the margin of the foramen magnum and a partial fusion of the posterior arch of the atlas with the occipital bone. A wide removal of the exposed occipital bone was done and the posterior arch of the atlas and fused second and third cervical spines excised. The dura mater was widely opened to reveal a gross abnormality at the junction of the medulla oblongata and medulla spinalis (fig. 4). At this level the gross narrowing of the canal had reduced the anterior posterior diameter of the neuraxis to a flattened band 2 to 3 mm. in thickness. The transverse diameter was also slightly reduced (11 mm. compared with 13 mm. at a lower level). In the neighbourhood of this gross constriction the nervous tissue lacked the normal vascular pattern and was ensheathed by a thickened layer of pia mater containing a plexus of small blood vessels. It was then noted that the uppermost cervical posterior root was directed laterally and superiorly from its attachment to the spinal cord at an acute angle to the point at which it penetrated the dura mater. So abnormal was its course that it was mistaken for the spinal accessory nerve until that nerve was seen lying anterior to the posterior root.

Post-operatively his progress was slow. However, headache was relieved and the bradypnœa which had caused anxiety cleared up. At follow-up examination twelve months after operation he had remained much as when discharged; he was, however, about to start work in spite of persistent weakness of the right hand with ataxia of all his limbs.

Case 5.—Summary. Occipital headaches followed by ataxia. Radiological diagnosis of basilar impression. Suboccipital craniectomy, removal of arch of atlas, and opening of the dura. Considerable post-operative improvement.

M. O'C., a woman aged 27, was admitted to St. Batholomew's Hospital on December 28, 1948. Six years previously she had started to have headaches which had gradually become more frequent and severe. There was a fairly constant frontal ache, and a more distressing pain occurred at the back of the neck and in the occipital region when she coughed, sneezed, laughed, or strained at stool. This pain came on immediately after coughing and lasted up to two hours. The severity of the pain was related to the intensity of the coughing or straining, severer attacks being accompanied by nausea and vomiting.

For two years there had been dizziness; this consisted of the objects at which she was looking moving about in front of her. This symptom was worse when the headache was severe For about two years also she had been unsteady when walking, tending to deviate to either side and at times actually falling when trying to walk. For a few weeks she had had a feeling of numbness in the upper part of the abdomen and there was occasional stress incontinence of urine. For two to three weeks prior to admission she had had a severe cough which aggravated the occipital headaches. She expectorated some sticky sputum which on one occasion had been streaked with blood.

On examination she had a broad forehead and a rather short neck (fig. 16). Passive movements of the neck were free and painless but on full flexion and on lateral movements she felt dizzy. There was a coarse rotatory nystagmus on lateral movements of the eyes and on looking down, but the other cranial nerves were normal. In the limbs tone and power were normal and there was no inco-ordination in the arms, but in the heel to knee test there was definite inco-ordination, more marked in the right leg than in the left.

All the tendon-jerks were pathologically brisk, the abdominal reflexes were absent, and the plantar responses were extensor. On sensory testing there was no cutaneous impairment: position sense was normal in the fingers and grossly impaired in the toes: vibration was appreciated normally on the fingers but was not felt on the anterior superior iliac spines, the patellæ, or the malleoli. When she walked there was marked ataxia with a tendency to deviate to either side. Romberg's sign was strongly positive.

Lumbar puncture gave a pressure of 85 mm. with a free rise to 300 mm. on bilateral jugular compression. C.S.F. was clear and colourless, and contained 1 lymphocyte per c.mm., protein was 20 mg. per cent, and there was no abnormality in the Lange curve. W.R. was negative in blood and C.S.F.

Radiological examination of the skull showed it to be broader than normal (fig. 17). The lateral edges of the foramen magnum were deeply invaginated into the skull with the posterior fossa forming a deep circle behind and lateral to the foramen. This appearance was shown well in tomograms (fig. 18). The foramen magnum was large with the first cervical vertebra lying partially within the foramen.

Radiological examination of the chest showed a diffuse opacity of part of the right upper lobe which was considered to be due to a pneumonitis. The sputum was negative for tubercle bacilli on 12 occasions. In view of the chest infection she was treated with penicillin and the pulmonary condition recovered rapidly. She was sent to a convalescent home and readmitted for operation on 28.3.49. There had been no significant change in her neurological condition during the interval.

On 25.4.49 a suboccipital craniectomy and removal of the posterior arch of the atlas was carried out with the patient in the sitting position. It was found that the region of the foramen magnum was deeply impressed into the skull, the displacement being more marked in connexion with the anterior part of the

foramen magnum than posteriorly. The occipital bone in the neighbourhood of the foramen was greatly thinned. Removal of the arch of the atlas revealed a well-marked constriction at the junction of spinal and posterior fossa dura mater. The dura was widely opened and the constriction divided to reveal a well-marked tonsillar herniation into the spinal canal. This herniation was thin and tongue-like, that on the right being bilobular. Separation revealed the medulla but the upper cervical roots were not displayed.

The post-operative course was uneventful and when discharged her headaches had greatly diminished and her walking improved. When she attended hospital for re-examination on 11.10.49 she had been well and had returned to work as a spinner. She was free from headache, was walking easily, though she was still subject to attacks of giddiness. Abnormal neurological signs found before operation were still present though less marked. The decompression was flat and soft.

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LEGENDS FOR PLATES

PLATE XX

FIG. 1.—Lateral film of normal skull showing Chamberlain's line and the basal angle.

PLATE XXI

FIGS. 5, 6 and 7.—Skull films of Case 1.

PLATE XXII

FIG. 8.—Ventriculogram in Case 1. The posterior defect in the shadow of the third ventricle is clearly seen and is due to a reversed tentorial pressure cone.

FIGS. 9 and 10.—Skull films of Case 2.

PLATE XXIII

FIGS. 11 and 12.—Photographs of Case 3.

FIG. 13.—Skull film of Case 3.

PLATE XXIV

FIGS. 14 and 15.—Films of skull and cervical spine of Case 4.

PLATE XXV

FIG. 16.—Photograph of Case 5.

FIGS. 17 and 18.—Skull films of Case 5.

PLATE XX

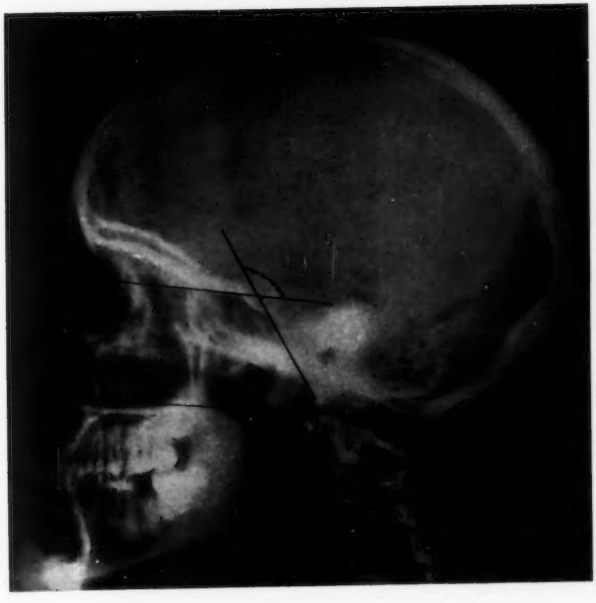

FIG 1.

To illustrate article by J. E. A. O'Connell and J. W. Aldren Turner.

FIG. 5.

FIG. 6.

FIG. 7.

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FIG. 8.

FIG. 9.

FIG. 10.

To illustrate article by J. E. A. O'Connell and J. W. Aldren Turner.

FIG. 11.

FIG. 12.

FIG. 13.

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FIG. 14.

FIG. 15.

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FIG. 16.

FIG. 17.

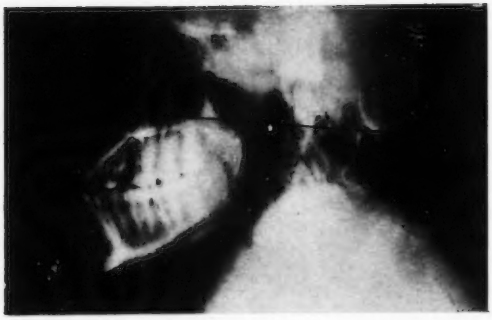

FIG. 18.

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Notices of Recent Publications

Selective Partial Ablation of the Frontal Cortex. By the Columbia-Greystone Associates. Ed. Fred. A. Mettler. 1949. Pp. xiv + 517. New York: Paul B. Hoeber, Inc. Price $10.00.

The interest of this work is provided by the fact that it was based on a controlled study. From a large hospital population a group of 48 patients were so selected as to provide 24 pairs, the two members of each pair matching the other in most important psychiatric characteristics. One member of each pair was then selected for operation, the control patients being chosen on such grounds as unwillingness for operation or some impairment of general health which increased the operative risk. All patients, subjects and controls, were chronically mentally ill people who had been judged incapable of improvement by any lesser measure than an operation on the brain. They varied in age from 20 to 61, in intelligence from I.Q. 55 to 131, and in occupation from labourer to research physicist. Nearly all (39) were suffering from schizophrenic psychoses, but there were 4 manic-depressives and 5 patients suffering from involutional psychoses. It was planned to remove sections of the frontal lobe from all the Brodman areas except 32 and 24, and to remove each of these areas more than once. In fact parts at least of the areas 6, 8, 9, 10, 11, 24, 44, 45, 46, and 47 were removed on one or more occasions. After the operation operative subjects and controls were treated as far as possible alike and in either case subjected to intensive efforts at rehabilitation. What is more important for this study, they were also all subjected to a great number and variety of physiological, psychological and psychiatric tests. The therapeutic results are interesting; 20 of the operated and 5 of the control subjects improved so far as to become parolable; 1 operated patient improved, though not to that degree; 3 operated and 19 control patients failed to improve.

The anatomical and physiological results are summarized by Dr. Mettler, in a mainly negative sense. He concludes that "any of the existing cytoarchitectural plans of the frontal cortex are sufficiently accurate to be used in accordance with the plan in question, and that mutual conversion between plans is possible." He comments on the wide variability in reported "functional deficits" resulting from operations on the frontal cortex, and notes that data have been gathered from wholly inequivalent surgical material. Commenting on the comparative results of experiments involving either stimulation or ablation, he notes that all stimulating procedures are highly artificial, while after ablation one does not observe the direct results of the ablation but the organism's compensatory behaviour. "Data obtained by stimulation are frequently falsely positive and . . . the appearance of intactness in organisms with actual organic damage is often deceptively negative." The data collected in the study show that removal of none of the Brodman areas by themselves or in the combinations used produces any notable permanent physiological effects, if area 4 and the most caudal part of area 6 are spared. Permanent paralytic phenomena did not follow, except for dysarthria and dysphagia after bilateral ablation of the inferior frontal gyri with possible injury to the foot of the precentral gyri or the cortex of the lateral cerebral fossa. Motor dysphasia did not invariably follow bilateral excision of the pars opercularis of the inferior frontal gyrus. Convulsions may follow, but did not invariably follow, removal of any specific area.

The psychological findings are almost equally negative. Dr. Landis concludes that no permanent psychological defects were detected by the methods they used.

With regard to temporary changes, the largest effects were associated with removal of area 6, decreasing as the site of removal was moved forward to area 11. Scores for reduction in "Anxiety and Complaint" were not related to the ablation of any particular area. Ablation of areas 11, 44 and 47 resulted in no regular psychological changes. There was no clear-cut evidence of a consistent or uniform personality change resulting from any particular variety of topectomy.

In discussing the psychiatric results, Dr. Heath emphasizes the effect of "total push." Five of the control patients actually did improve, and could not have been expected to do so otherwise. He is rather more positive about differential results than his co-authors and says that "only in patients in whom improvement was felt to be definitely related to operation had areas 9 and 10 been implicated in the removal. In the 9 patients who did not have parts or all of the areas included at operation, psychotic behaviour was not altered." There was no correlation between improvement on the one hand and the amount of tissue removed, abnormality in the post-operative EEG, or transient physiological disturbances on the other. Patients with well-preserved affect responded best, regardless of the diagnostic category; and otherwise the duration of the illness was not important.

The work is a valuable and comprehensive contribution, guided by a healthy conservatism, particularly in regard to the results claimed. It is not easy to suggest, in the present state of our knowledge, ways in which the ordering of the experiment could have been improved. From the psychological point of view, where one of the main sources of interest lies, the tests used were well selected and covered a wide range of performance. A valuable feature is the demonstration that in some tests no change after operation may be compared with improvement on retesting the control group, suggesting an actual change in performance of the operated group. At the same time, the study shows the limitation of the test battery, and of preoccupation with mean performances rather than analysis of individual results. In a group consisting of such heterogeneous clinical material with great variation in the lesion inflicted, there is a likelihood that real change may be obscured in the computation of averages. There is a strong possibility that cortical ablation may impair some basic function essential to the performance of the test, rather than the more complex function which the test measures in normal subjects; and that some such basic function may underlie tests which in normals seem to measure widely different functions. This may explain Landis's comment that change on one test does not produce changes in other tests which in normals apparently measure the same function. The rather disappointing results obtained by this carefully planned group experiment suggests that the time is still one for more individualized study.

Psycho-Analysis. A Handbook for Medical Practitioners and Students of Comparative Psychology. By EDWARD GLOVER. Second Edition. 1949. Pp. 367. London: Staples Press. Price 15s.

In his introductory chapter, the author makes an interesting attempt to bring the concepts of psychoanalysis into a meaningful relation with those of physiology. Mind, being the central system of a reflex arc, can be regarded as an instrument or apparatus and as having a psychic locality and structure. This structure can be subdivided into a number of component parts or mental institutions. This is the topographic approach. The dynamic approach is concerned with the excitations which disturb the central system. Mental activity is a response to disturbances of equilibrium arising out of the stimulations of unsatisfied instincts and the psychic discomforts which follow or threaten to follow rise or fall of instinctual energy. Activities due to instinct tension may show themselves as thoughts or feelings or appear as bodily innervations, e.g. in behaviour. There is also an economic aspect. The mind seeks to reduce stimulation to an optimum level, and in the case of

undischarged excitations, does so through unconscious mechanisms. They may provide a substitute discharge, or may distribute the excitation over qualitatively different systems, or may inhibit the energy as near as possible to source. Neuroses and mental disorders are simply forms of unsatisfactory discharge.

It cannot be doubted that abnormalities of the mental functions of the organism will one day be brought into relation with our basic knowledge of neurophysiology; but this hardly seems the way to do it. The reader is brought up with a start at the first postulate: mind as the central system of a reflex arc. The physiologist must, surely, retort that mind is a *function* of the central system of a reflex arc (if the arc can be used in such a wide sense) and in consequence it cannot be usefully thought of as having either locality or structure. When we go on to subdivision we reach a second difficulty. A structure may be subdivided by its topographic limits, or its connexions and relations with neighbouring parts. A function can only be subdivided arbitrarily by considering in turn its several aspects or qualities, or its relation to different structures. Every step in Dr. Glover's exposition leads to similar difficulties of a fundamental kind.

The theory of psychoanalysis, which is extremely complex, is expounded by Dr. Glover with comprehensiveness and authority. But doubts arise whether, on so semantically unsatisfactory a basis, it can possibly be scientifically sound. Primitive peoples, in awe at what they beheld, deified the processes of nature into gods of sea and river and sky, with a topography, a dynamism and an economy of their own. We have succeeded in understanding a little more than they by regarding as structures only those things with a material existence bounded in space, and by trying to describe processes and functions in different terms.

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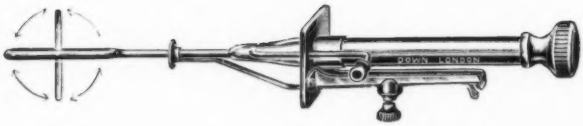

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